ORAL ASSUMPTION OF BENZYDAMINE-CONTAINING VAGINAL PREPARATIONS IN ASSOCIATION WITH TV ADVERTISING IN ITALY: ANALYSIS OF CASES HANDLED BY A NATIONAL POISON CONTROL CENTRE

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ORAL ASSUMPTION OF BENZIDIDAMINE-CONTAINING VAGINAL PREPARATIONS IN ASSOCIATION WITH TV ADVERTISING IN ITALY: ANALYSIS OF CASES HANDLED BY A NATIONAL POISON CONTROL CENTRE

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ABSTRACT

Objective To document the impact of a TV advertising campaign on safe use of non-prescription vaginal preparations in Italy.

Design An interrupted time series design with data routinely collected by the National Poison Control Centre of Milan. Analysis of 187 cases of hazardous exposure to benzydamine-containing vaginal preparation occurred from January 2005 to December 2010 (providing five years data for the *pre-advertising* period, two and a half months data for the *advertising* period, and ten months data for the *post-advertising* period) using observed/expected ratios and comparing characteristics of cases in the different periods by means of Pearson's χ^2 test.

Results: In the *advertising* period the observed number of women-related cases was about 23 times higher than expected (22.9, 95% confidence interval 17.6 to 29.2), while men related-case were about four times higher than expected (3.7, 0.8 to 11.0). In the *post-advertising* period the occurrence of cases was about five times higher than expected (5.1, 3.8 to 6.6) in women and as expected in men. In comparison to the *pre-advertising* period, the *advertising* and *post-advertising* periods were characterized by an increased proportion of exposures due to confusion about the correct administration route (16% *v* 81 and 55%, respectively), and of cases reporting signs and symptoms related to the exposure (27% *v* 55 and 42%, respectively).

Conclusions: TV advertising of benzidamina-containing vaginal preparations was associated in Italy to a dramatic increase in the occurrence of unintentional oral exposure to these drugs. In particular, the available data showed a short- and long-term misleading effect of the TV message on the correct admistration route.

The observations here reported provide an example of how TV advertising can negatively affect safe use of non-prescription drugs, highlighting the need of monitoring reports on therapeutic errors and adverse effects before, during, and after direct to consumer promotion of specific preparations.

ARTICLE SUMMARY

Article focus

The study is focused on documenting the impact of a TV advertising campaign on safe use of benzydine-containing vaginal preparations in Italy.

Key messages

Advertising campaign can affect safe use of medicine preparations. Selected outcomes, such as therapeutic errors, should be attentively monitored before, during, and after advertising campaigns on specific medicines. A particularly relevant contribution to this type of activity can be provided by national Poison Control Centres.

Strengths and limitations

The article is based on routinely collected and readily available data which documented the immediate effects of TV advertising on safety use of specific medicines. The main limitition derives from lack of information on marketing trends in association with TV promotion.

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Competing interest

All authors have completed the Unified Competing interest form at www.icmje.org/coi-disclousure.pdf (available on request from the corresponding author) and declare that all authors had: (1) No financial support for the submitted work as declared above; (2) No financial relationships with commercial entities that might have an interest in the submitted work; (3) No spouses, partners, or children with relationships with commercial entities that might have an interest in the submitted work; (4) No non-financial interests that may be relevant to the submitted work.

Introduction

Benzydamine hydrocloridrate (BHC) (CAS nr 132-69-4) is a local anti-inflammatory and analgesic active ingredient synthesised by Angelini research laboratories in mid 1960. Since then, preparations containing BHC have been marketed worldwide for symptomatic treatment of oro-pharyngeal and gynaecological conditions (1). The available data indicate that topical applications of BHC are usually well tolerated, with infrequent side-effects (2). Absorption through skin and mucosa is low, while BHC is rapidly absorbed in the GI tract (3,4). In humans, acute overdose can cause nausea, vomiting, visual hallucinations, oesophageal irritation, agitation and somnolence (5-8). Injuries due to BHC exposure have been mainly associated to oral assumption of vaginal preparations caused by confusion about the correct administration route and by their being mistaken for oral antiseptic preparations (8). A few reports on abuse have been also reported (7,9).

In Italy, between 1977 and 2009, BHC containing vaginal preparations had been classified as pharmacy-supervised drugs (sold under the supervision of a pharmacy), a category of non-prescription medicines for which direct to consumer advertising (DTCA) is not allowed. In mid 2009, these preparations were switched to the category over-the-counter (OTC), allowing for DTCA. Between December 20, 2009 and January 2, 2010, the producer launched a first intensive TV advertising campaign, followed by a second one, launched from January 17 to 23. Immediately after the first campaign, the national Poison Control Centre of Milan (PCCM) observed a sharp increase in the number of consultations referred to cases of unintentional oral ingestion of BHC containing gynaecological preparations. Taking into account this observation, the Italian Ministry of Health required a revision of the TV spot in order to improve the information concerning the topical use of the preparations. A new campaign was launched between February 21 and 27, 2010, and in this case the spot included a statement on the topical use of the medicine. Afterwards, the TV advertising was voluntary stopped by the producer.

Aim of the present paper is to document how the occurrence of cases exposed to BHC containing vaginal preparations has changed in Italy in association with TV advertising campaigns.

Materials and methods

PCCM handles yearly about 42.000 new cases of human exposures, accounting for more than 60% of all cases referred to all the PCCs active in Italy (12). For each patient examined, PCCM uses a standard form to collect the following main categories of data: demographic characteristics; exposure characteristics (i.e., reason for exposure, latency between exposure and clinical effects; therapy; type of outcome). The database of the national PCCM was searched retrospectively (from January 1, 2005 to 31 December, 2010) and prospectively (from January 1, 2010 to 31 December, 2010) in order to identify all cases exposed to BHC containing vaginal preparations. A clinical toxicologist reviewed the available information for each case of interest and determined if the case was symptmatic and whether the reported outcomes could be related to BHC exposure. Severity of clinical outcomes asssociated to BHC exposure was graded according the Poisoning Severity Score (11). For purposes of analysis, the identified cases were classified into three groups taking into account the exposure period, i.e., *pre-advertising* period (period of time *before* the advertising campaign), between January 1, 2005 and December 19, 2009; *advertising* period (period of time *during* the advertising campaign), between December 20, 2009 and February 27, 2010, when the TV campaign was repeatedly launched, plus the week following the last day of transmission (February 28-March 6), assuming that the effect of advertising was still acting; *post-advertising* period (period of time *after* the advertising campaign), between March 7 and December 31, 2010.
The mean number of cases of exposure/day by gender and period, along with 95% confidence intervals (95%CI) were calculated assuming a Poisson's process. The mean rates in the *pre-advertising* period were assumed to be constant over time and used to estimate expected cases in the *advertising* and *post-advertising* periods. The observed/expected (O/E) case ratio was used as a measure of association between exposure rates and TV advertising. The O/E ratios' 95%CIs were derivated assuming a Poisson's process for the observed cases (10). Furthermore, the main characteristics of cases in the three periods were compared by using Pearson's χ^2 test.

Results

Altogether, 216 cases exposed to BHC containing vaginal preparations were identified. Among them, 88 occurred in the five year *pre-advertising period,* 67 and 61 in the *advertising* and *post-advertising* periods, respectively (Table 1). The occurrence of exposure by year and month is shown in Figure 1. In the *pre-advertising* period, the total number of exposures ranged between 15 and 20 cases/year and between 0 and 4 cases/month. A sharp increase in the absolute number of cases was observed during the first and second launch of the TV advertising campaign, with 20 cases occurred between December 20-31, 2009, and 31 cases in January 2010. In February, 12 cases were observed, 7 of which occurred during the last TV advertising campaign (February 21-27) (Figure 2). Twelve cases were also identified in March, 4 of which occurred within the first 6 days of the month, also included in the *advertising* period. In the following months, the number of cases ranged between 3 and 11.

In the *pre-advertising* period, 67 cases occurred in women, accounting for 0.04 cases/day, 95% confidence intervals 0.03 to 0.05, and 20 cases occurred in men (0.01 cases/day, 0.01 to 0.02). According to those rates, in the *advertising* period about three women and one man were expected, while the observed cases were 64 (O/E 22.9, 17.6 to 29.2) and three (O/E 3.7, 0.8 to 11.0), respectively. In the *post-advertising* period the expected cases were about 11 in women and 3 in men. The observed cases were still significantly higher than expected in women (n=56, O/E 5.1, 3.8 to 6.6), but close to the expected number in men (n=5, O/E 1.5, 0.5 to 3.5) (Table 1).

The distribution of cases by gender and exposure period showed an increased percentage of women in the *advertising* and *post-advertising* period (92%, respectively) in comparison to those reported in the *pre-advertising* one (72%, Pearson's $\chi^2 = 6.29$, P=0.043). Focusing the attention on women, in the *advertising* period, the proportion of cases treated at hospital (52%) was slightly higher in comparison to those reported in the *pre-advertising* (42%) and *post-advertising* period (43%). However, these differences were not statistically significant. Cases occurred in the *pre-advertising* and *advertising* periods showed statistically significant different distributions by class of age (Pearson's $\chi^2 = 22.10$, P=0.001), reason for exposure (Pearson's $\chi^2 = 69.70$, P<0.000), and severity of outcomes (Pearson's $\chi^2 = 11.50$, P=0.003). In particular, the *advertising* period was characterized by a predominance of subjects aged 20-49 years (77% *v* 46%), therapeutical errors due to incorrect route of assumption (81% *v* 16%), subjects with BHC related outcomes (56% *v* 27%) in comparison to the *pre-advertising* one. In the *post-advertising* period, the distribution of cases by age was comparable to that reported in the *pre-advertising* period, while statistically significant differences were still reported for distribution of cases by reason for exposure (Pearson's $\chi^2 = 20.76$, P<0.000), and severity of outcomes (Pearson's $\chi^2 = 10.61$, P=0.005).

Altogether, 88 cases suffered BHC related clinical effects. Among them, severity of outcomes was low in 77 cases (87%) and moderate in 11 (13%). No cases reported outcomes of high or fatal severity. All cases of moderate severity were women. One of these cases was exposed in the *pre-advertising* period, 4 and 5 in the *advertising* and *post-advertising* periods, respectively. All cases of moderate severity were due to therapeutic errors. More specifically, the exposure was caused by incorrect administration route in 7 cases and by confusion with other medicine in three. The outcomes most frequently associated to BHC exposure included: vertigo (n=26), oropharyngeal irritation (n=19), heartburn (n=25), vomiting (n=19), nausea (n=14), pharingeal pain (n. 6), hallucinations (n=7), headache (n=6) (Table 2).

Comments

In Italy, TV advertising of BHC containing vaginal preparations was associated to a dramatic increase in the occurrence of unintentional oral exposure to these drugs. This observation could be associated to an increased number of users (population at risk of exposure). As a matter of fact, according to the data provided by the producer, in December 2009 the number of packets sold out was more than two times higher than that reported in November 2009 (173,724 *vs* 83,745). Assuming that during the first 20 days of December the number of packets sold out by day was comparable to that occurred in November (about 2,800 packets/day), and considering that the observed marketing increase was driven by TV advertising, about 15,000 packets/day could have been reasonably sold out during the last 10 days of December 2009, accounting for a five times increase. During the same ten day period the PCCM handled 20 cases of exposure while in the previous twenty days it observed only three cases. Furthermore, the main characteristics of cases referred to the PCCM for toxicological advice following exposure to the advertised preparations changed abruptly immediately after TV DTCA. In particular, the available data showed an immediate effect of advertising on age composition of users, with an increased predominance of young adult women, to whom the TV spot was specifically addressed, and an increased proportion of exposures due to confusion about the administration route. This last observation strongly suggests that the TV message was misleading or did not provide adequate information on topical application of the drugs. Although the occurrence of cases was decreased in the *post-advertising* period in comparison to the *advertising* one, the proportion of exposures due to incorrect administration route remained higher than that observed in the *pre-advertising* period , suggesting a long-term effect of advertising on the medicines improper use.

The impact of DTCA on safety profile of medicines has been poorly investigated (13). The observations here reported document how DTCA can negatively affect the correct use of OTC, highlighting the need of monitoring selected outcomes, such as therapeutic errors and adverse effects, before, during, and after advertising campaigns. A particularly relevant contribution to this type of activity can be provided by national PCCs.

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Figure 1. Distribution by year and month of cases of exposure to BHC containing vaginal preparations referred to the national Poison Control Centre of Milan for toxicological advice in 2005-2010

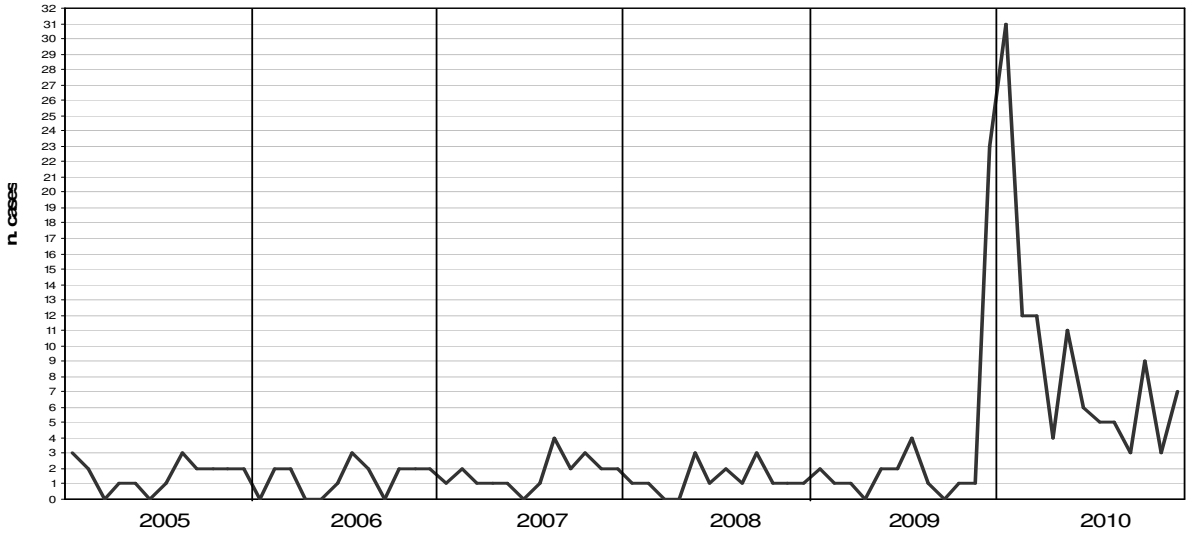

Figure 2. Daily number of cases of exposure to BHC containing vaginal preparations referred to the national Poison Control Centre of Milan from December 2009 to August 2010

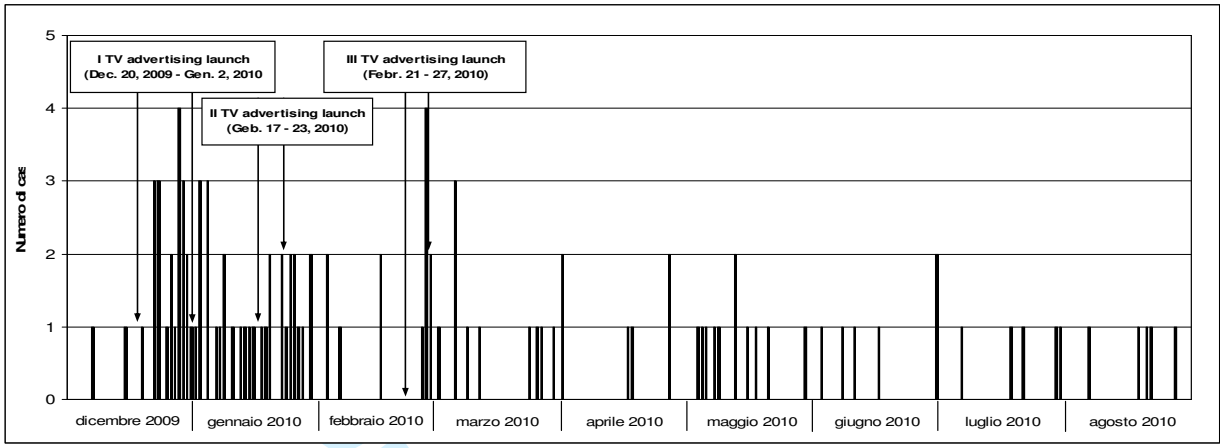

Table 1. Mean daily rates and observed/expected ratios of cases exposed to BHC containing vaginal preparations referred to the national Poison Control Centre of Milan in 2005-2010

	Women						Men					
Period	Mean cases/day	95%CI	Obs.	Exp.	O/E	95%CI	mean cases/day	95%CI	Obs.	Exp.	O/E	95%CI
Pre-advertising *Jan.1,2005-Dec.19,2009*	0.04	0.03-0.05	67	-	-	-	0.01	0.01-0.02	20	-	-	-
Advertising *Dec.20,2009-Mar.6,2010*	0.83	0.62-0.91	64	2.8	21.8	16.7-24.8	0.04	0.01-0.11	3	0.8	3.7	0.8-11.0
Post-advertising *Mar.7-Dec.31,2010*	0.19	0.14-0.24	56	11.1	5.1	3.8-6.6	0.02	0.01-0.04	5	3.3	1.5	0.5-3.5

Table 2. Main characteristics of women exposed to BHC containing vaginal reparations referred to the national Poison Control Centre of Milan in 2005-2010

	Period							
	Pre-advertising (67 cases)		*Advertising* (64 cases)			*Post-advertising* (56 cases)		
	n.	%	n.	%	P*	n.	%	P*
Site of call for assistance					0.294			0.932
Hospital	28	41.8	33	51.6		24	42.9	
Private residence	24	35.8	15	23.4		21	37.5	
Other	15	22.4	16	25.0		11	19.6	
Age (years)					0.003			0.777
< 5	6	8.9	0	0.0		3	5.4	
5 – 19	14	20.9	4	6.2		9	16.1	
20 – 34	21	31.3	33	51.6		20	35.7	
35 – 49	10	14.9	16	25.0		12	21.4	
50 +	14	20.9	10	15.6		9	16.1	
Unknown	2	3.0	1	1.6		3	5.4	
Reason for exposure					<0.001			<0.001
Unintentional-General**	21	31.3	4	6.2		8	14.3	
Unintentional-therapeutic error								
medicine exchange	35	52.2	8	12.5		17	30.4	
incorrect route	11	16.4	52	81.2		31	55.4	
Preparation								
500 mg granular form	65	97.0	60	93.8		47	83.9	
Others	1	2.3	3	4.7		9	16.1	
Unknown	1	1.1	1	1.6		0	0.0	
Severity of outcomes					0.001			0.005
None	49	73.1	28	43.7		27	48.2	
Minor	17	25.4	31	48.4		22	39.3	
Moderate	1	1.5	4	6.2		7	12.5	
Signs/symptoms								
Vertigo	6	8.9	12	18.7		8	14.3	
Oropharyngeal irritation	7	10.4	11	17.2		1	1.8	
Heartburn	3	4.5	9	14.1		13	23.2	
Vomiting	5	7.5	5	7.8		9	16.1	
Nausea	3	4.5	7	10.9		4	7.1	
Pharyngeal pain	2	3.0	4	6.2		0	0.0	
Hallucinations	1	1.5	3	4.7		3	5.4	
Headache	0	0.0	4	6.2		2	3.6	
Other	6	8.9	9	13.4		12	21.4	

* Comparing with the *pre-advertising* period by using Pearsons' χ^2 test or Fisher's exact test; *Including cases who exchanged BHC solution for drinking water or other beverages.

Contributors: LS developed the research proposal, planned the study design and the analysis, drafted and edited the paper. FD was responsible for data collection, assessed severity of cases, and contributed to editing the paper. LL contributed to planning the analysis, undertook the analysis, and contributed to drafting and editing the paper. MLC and FF contributed to editing the paper and are guarantors

Checklist of items included in the study

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ORAL ASSUMPTION OF A TOPICAL BENZYDAMINE-CONTAINING GYNAECOLOGICAL PREPARATION IN ASSOCIATION WITH TELEVISION ADVERTISING IN ITALY: ANALYSIS OF CASES MANAGED BY A NATIONAL POISON CONTROL CENTRE

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Funding	22		

ORAL INGESTION OF A TOPICAL BENZYDIDAMINE HYDROCHLORIDE-CONTAINING GYNAECOLOGICAL PREPARATION IN ASSOCIATION WITH TELEVISION ADVERTISING IN ITALY: ANALYSIS OF CASES MANAGED BY A NATIONAL POISON CONTROL CENTRE

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ABSTRACT

Objective: To evaluate the impact of a television advertising campaign on the risk of oral ingestion of a topical non-prescription gynaecological preparation containing benzydamine hydrochloride.

Design: We analysed cases of exposure to the preparation reported to the National Poison Control Centre in Milan from January 2005 to December 2010. This period was divided into three separate periods: *pre-advertisement* (five years); *advertisement* (two and a half months); and *post-advertisement* (ten months). The periods were compared in terms of the observed/expected ratio of cases, with expected cases based on data from the *pre-advertisment* period and adjusted for variations in the number of users, estimated based on sales. The main characteristics of cases were compared for the three periods using Pearson's χ^2 test or Fisher's exact test..

Results: During the study period, 216 cases of ingestion of the preparation were reported. The adjusted observed/expected ratio of cases of ingestion in women was 7.48 (95% confidence interval: 5.76 to 9.56) in the *advertisement* period and 2.97 (95% CI: 2.24 to 3.85) in the *post-advertisemen*t period. Regarding the characteristics of cases, there was an increased proportion of cases of expsoure due to confusion about the correct administration route in the *advertisement* and *post-advertisement* periods (81% and 55%, respectively, compared to 16% for the *pre-advertisement* period.) and of individuals with signs and symptoms related to exposure (55%, 52%, and 27%, respectively).

Conclusions: In Italy, an advertisement for a non-prescription medicine seems to have confused consumers regarding the adminstration route. This effect was observed even after the advertisement had stopped being broadcast. These results highlight the need for the monitoring of medication errors and adverse effects before, during, and after advertising.

ARTICLE SUMMARY

Article focus

The study is focused on documenting the impact of television advertising on the safe use of benzydamine hydrochloride-containing gynaecological preparations in Italy.

Key messages

Advertising can affect the safe use of medicine. Select outcomes, such as medication errors, should be carefully monitored before, during, and after advertising campaigns. To this end, poison control centres can be extremely useful.

Strengths and limitations

The study is based on routinely collected and readily available data (i.e., reports and telephone calls made to a national poison control centre), which allowed for the comparison of the main characteristics of cases of dangerous exposure to a medicine and for the evaluation of the association between the occurrence of cases and a television advertising campaign. The main potential limitation is that the data were provided on a voluntary basis to the poison control centre, so that they may not be representative of all cases occurring in the general population.

Funding

This research received no specific grant from any agency in the public, private, or non-profit sectors.

Competing interest

All authors have completed the Unified Competing Interest form at www.icmje.org/coi-disclousure.pdf (available on request from the corresponding author) and declare that all authors had: (1) No financial support for the submitted work as declared above; (2) No financial relationships with commercial entities that might have an interest in the submitted work; (3) No spouses, partners, or children with relationships with commercial entities that might have an interest in the submitted work; (4) No non-financial interests that may be relevant to the submitted work.

Introduction

Benzydamine hydrochloride (BHC) (CAS no. 132-69-4) is a local anti-inflammatory and analgesic active ingredient first synthesised by the Angelini research laboratories in the mid-1960s. Since then, topical preparations containing BHC have been marketed worldwide for the symptomatic treatment of oropharyngeal and gynaecological conditions (1). These preparations are sold as concentrated or ready-to-use solutions or as a powder to be dissolved in water. Topical preparations of BHC are usually well tolerated, with infrequent side-effects (2). Absorption through the skin and mucosa is low, whereas experimental data indicate that BHC is rapidly absorbed in the GI tract (3,4). A limited number of reports on acute oral exposure in humans have shown that BHC overdose can cause nausea, vomiting, visual hallucinations, oesophageal irritation, agitation and somnolence (5-8). These effects have resulted mainly from the ingestion of gynaecological preparations because of confusion about the correct administration route and the preparations' being mistaken for oral medicines (8). A few cases of injuries due to intentional ingestion for recreational use have also been reported (7,9).

In Italy, from 1977 to 2009, BHC-containing gynaecological preparations manufactured by Angelini were classified as pharmacy-supervised drugs (sold under the supervision of a pharmacy), a category of non-prescription drugs for which direct to consumer advertising (DTCA) is prohibited. In April 2009, these preparations were reclassified as over-the-counter (OTC) drugs with the following therapeutic indications: vulvovaginitis of any origin or nature, characterised by small vaginal discharge, itching, irritation, burning, and vulvar pain; and personal hygiene during puerperium. The label on the package was changed from "vaginal solution" to "cutaneus solution for external genital organs" (10). Given the drug's new status, DTCA was allowed, and the manufacturer launched an intensive television advertising campaign between December 20, 2009 and January 2, 2010, followed by a second campaign between January 17 and 23, 2010. The advertisement focused on solidarity among women and on their ability to solve their "intimate

problems" by using the advertised preparation. At the end of the advertisement, an allusion was made to the mode of use, with a woman's silhouette with concentric circles on the abdomen.

During the first television campaign, the National Poison Control Centre in Milan (PCCM) observed an unexpectedly increased number of requests for assistance for cases of unintentional oral ingestion (i.e., from approximately 1 case per month to 2 cases per day). Based on these findings, the Italian Ministry of Health required that the advertisement be revised to clarify that the product was for topical use. The advertisement was rebroadcast between February 21 and 27, 2010, with a written statement at the end of the advertisement stating that the preparation was for topical use only and a woman's silhouette with concentric circles on the pubis area. Afterwards, the advertisement was voluntarily stopped by the manufacturer. The objective of the present study was to document how unintentional oral exposure to BHC-containing gynaecological preparations was inadvertently promoted by television advertising in Italy.

Materials and methods

Each year the PCCM receives approximately 42,000 reports of human exposure to different types of substances (11), accounting for more than 60% of all cases referred to Italian PCCs (12). The PCCM mainly provides consultation to hospitals (60% of cases) and to the general public (30% of cases) throughout Italy. Assistance for diagnosing and treating poisonings is provided by medical toxicologists, mainly over the phone. For each case, the toxicologist collects the following data in real-time using a standard form: demographic characteristics; exposure characteristics (e.g., substance/commercial product, route of exposure, reason for exposure, dose, and latency between exposure and onset of clinical effects); signs and symptoms; therapy; and outcome. About 45% of the human exposures managed by PCCM are medicine-related; of these, about 17% of these individuals are victims of the inappropriate use of medication (13).

For the present study, the PCCM database was searched from January 1, 2005 to December 31, 2010 to identify all cases of inappropriate exposure to the BHC-containing gynaecological preparation, which is available in diverse forms (i.e., concentrated solution, ready-to-use solution, and powder). A clinical toxicologist (FD) reviewed the available information for data consistency and to grade the severity of outcome according to the Poisoning Severity Score (i.e., *none*, no signs/symptoms; *minor*, mild, transient, and spontaneously resolving signs/symptoms; *moderate*, pronounced or prolonged signs/symptoms; *severe*, life-threatening signs/symptoms or resulting in significant residual disability or disfigurement; *fatal*, death as a result of exposure or of direct complications of the exposure effects) (14). For the purposes of the present analysis, the identified cases were classified into three groups based on exposure period: i) the *pre-advertisement* period (i.e., from January 1, 2005 to December 19, 2009), before the advertisement was broadcast; ii) the *advertisement* period (i.e., from December 20, 2009 to February 27, 2010), when the advertisement was repeatedly launched, plus the week following the last day of broadcast (i.e., from February 28

to March 6, 2010), assuming that the advertisement still had an effect; and iii) the *post-advertisement period* (i.e., from March 7 to December 31, 2010).

The mean number of packages sold per day during these periods was estimated based on the number of packages sold per month in the period from November 2009 to October 2010 (information provided by the manufacturer). We assumed that the sales during the *pre-advertisement* period remained constant; we thus decided to calculate the mean number of packages sold per day based on sales in November 2009 (2,791 packages/day). Since the first 20 days of December were included in the *pre-advertisement* period, the quantity sold in these 20 days was based on sales in November 2009 (55,820 packages). This value was subtracted from the total number of packages sold in December. The remaining quantity (117,904 packages) was used to estimate the mean number of packages/day sold in the period December 21-31 (n=10,718) under the assumption that the observed increase was completely driven by advertising. During the entire *advertisement* period, an estimated mean of 8,381 packages/day were sold, whereas in the *post-advertisement* period a mean of 4,764 packages/day were sold. The ratio of *advertisement*-period sales *to pre-advertisement* sales and the ratio of *post-advertisement* sales to *pre-advertisement* sales were calculated as an indicator of the increased number of users (i.e., the population at risk of exposure). These ratios corresponded to a 3.0-fold mean increase in the *advertisement* period (range, by calendar month: 2.1 to 3.8) and a 1.7-fold mean increase in the *post-advertisement* period (range, 1.2 to 2.1).

The mean daily rate (i.e., the mean number of cases of exposure/day) by gender and period was calculated, as were the 95% confidence intervals (95% CI), assuming a Poisson's process. In the *pre-advertisement* period, the mean daily rate for both men and women was assumed to be constant over time and used to estimate the expected number of cases in the *advertisement* and *post-advertisement* periods. These expected values were adjusted by the estimated increases in the population at risk of exposure in the two periods. The ratio of observed to adjusted expected cases (O/E) was used as a measure of the association between inappropriate exposure and television

advertising. The 95% CIs of the O/E ratio were derived assuming a Poisson's process for the observed cases (15). The main characteristics of cases in the three periods were compared using Pearson's χ^2 test or Fisher's exact test.

Results

A total of 215 cases of oral exposure to the advertised gynaecological preparations were identified. Of these, 187 were women and 28 were men. All cases were unintentionally exposed through oral ingestion, with the exception of one man who intentionally ingested the preparation.

The mean number of cases/day observed by month in the three different periods is shown in Figure 1; the mean number of packages sold per day is also shown. In the *pre-advertisement* period, there were 15-20 cases/year and 0-4 cases/month. The mean number of cases/day by month ranged from 0.00 to 0.15. In the *advertisement* period, 1.85 cases/day were observed during the last 10 days of December, which were completely covered by the first advertising campaign. In January, 1.00 cases/day were observed; the beginning of this month was covered by the first advertising campaign, which was broadcast until January 2nd, and, subsequently, from January 17th to 23rd by the second advertising campaign. In February, 0.48 cases/day were observed; the third advertising campaign was broadcast from February 23rd to 27th. The estimated number of packages sold per day varied from 10,718 in the last ten days of December, to 6,142 in January, and 5,788 in February. During the *post-advertisement* period (i.e., from March 7 to December 31, 2010), the mean number of cases/day ranged from 0.10 to 0.35. The estimated number of packages sold per day ranged from 6,000 to 3,373.

The distribution of cases by gender and period and the corresponding daily rates are shown in Table 1. The observed/expected ratios, adjusted by the estimated increase in the population at risk of exposure (i.e., 3.0- and 1.7-fold increase in the *advertisement* and *post-advertisement* period, respectively) are also shown. In the *pre-advertisement* period, 67 cases occurred in women, accounting for 0.04 cases/day (95% CI, 0.03 to 0.05) and 20 cases occurred in men (0.01 cases/day, 95% CI 0.01 to 0.02). In the *advertisement* period, in women, there were 64 observed cases and 8.55 expected cases (O/E 7.48, 95% CI, 5.76-9.56), whereas in men the observed cases were close to the expected ones (3 *vs.* 2.54, O/E 1.18, 95% CI, 0.24-3.45). In the *post-advertisement* period, in

women, there were 56 observed cases and 18.87 expected cases (O/E 2.97, 2.24 to 3.85). In men, there were 5 observed cases and 5.63 expected cases (O/E 0.89, 0.29 to 2.07).

The main characteristics of female cases by period of exposure are reported in Table 2. In the *advertisement* and *post-advertisement* periods, the percentage of females (95 and 92%, respectively) was significantly higher than that in the *pre-advertisement* period (76%, P=0.001 and 0.025, respectively). The percentage of individuals who were hospitalised in the *advertisement* period (52%) was slightly higher, though not significantly, than that in the *pre-advertisement* (42%) and *post-advertisement* (43%) periods. When comparing cases in the *pre-advertisement* and *advertisement* periods, significantly different distributions were found for age class (P=0.003), reason for exposure (P<0.001), and medical outcome (P=0.002). In particular, the *advertisement* period, compared to the *pre-advertisement* period, was characterized by a predominance of cases aged 20-49 years (77% *v* 46%), medication error due to misunderstanding of the correct mode of use (81% *v* 16%), and individuals suffering BHC-related effects (55% *v* 27%). In the *post-advertisement* period, the distribution of cases by age was comparable to that reported in the *pre-advertisement* period, whereas significant differences were found for the distribution of cases by reason of exposure (P<0.001) and medical outcomes (P=0.005).

Altogether, 82 women exhibited BHC-related effects. The severity of medical outcomes was minor in 70 women (85%), and moderate in 12 (13%). No severe or fatal effects were observed. The signs and symptoms most frequently associated with BHC ingestion included: vertigo (n=26), oropharyngeal irritation (n=19), pyrosis (n=25), vomiting (n=19), nausea (n=14), pharyngeal pain (n=6), hallucinations (n=7), and headache (n=6) (Table 2).

With reference to men exposed in the *pre-advertisement* period (n=20), 50% mistook a BHC solution for drinking water or other beverage, whereas for the remaining 50% the exposure was due to confusion with other medicine. Similarly, in the *advertisement* period, two cases reported having mistook a BHC solution for a beverage and one for another medicine. Among the five cases detected in the *post-advertisement* period, in one case the exposure was due to intentional abuse;

one case each mistook the solution for a beverage or another medicine. Altogether, 6 patients were symptomatic and suffered oropharyngeal irritation (n=3) and vomiting (n=3).

Comments

In the European Community, DTCA is only allowed for medicinal products that are classified as "not subject to medical prescription" (16), commonly referred to as "OTC". This classification should be based on an evaluation of the balance between the potential benefits of the product's being readily available for self-treatment and the potential harm resulting from unsupervised or inappropriate use. Thus the safety of OTC medicines needs to be continuously monitored, to identify unforeseen problems and implement suitable interventions to minimise the potential for harm (17-19).

DTCA is a source of information that tends to emphasise the beneficial effects of the advertised product (20), which could inadvertently contribute to unnecessary or inappropriate use. However, the impact of DTCA on the safe use of non-prescription medicines has only been studied to a limited extent (21,22). Some studies have shown that self-medication of vaginal conditions with OTC antifungal preparations is associated with unnecessary use and a delay in proper diagnosis and treatment (23,24). With specific regard to BHC-containing gynaecological preparations, a study in Spain has shown a high frequency of medication error due to misunderstandings about the correct administration route (8).

In Italy, until April 2009, BHC-containing gynaecological preparations had been classified in a category of medicines that can be obtained without a prescription yet for which DTCA is not allowed. The re-classification as "OTC" was not associated *per se* with an increase in cases of exposure (Figure 1) or with changes in the case distribution by gender or other characteristics. Instead, the daily rate of cases of exposure reported to the National PCCM increased abruptly in association with television advertising, and this increase can be explained only in part by the increased number of users. In particular, during the first advertising campaign (i.e., December 20, 2009 - January 2, 2010), there was a 17.5-fold increase in the daily rate of cases of oral exposure compared to the *pre-advertisement* period, but only a 3.8-fold increase in the number of users; when

adjusting for the number of users, there was still a 9.5-fold increase in the daily rate of cases. The analysis of the observed/expected ratio, which was performed taking into account a mean 3.0-fold increase in the number of users during the *advertisement* period, showed a statistically significant 7.5-fold increase in the risk of exposure in association with advertising. In the *post-advertisement*-period, when the estimated number of users was on average 1.7-fold higher than that in the *pre-advertisement* period, the risk of exposure was approximately 3 times higher than that in the *pre-advertisement* period, suggesting that the advertisement had a long-lasting effect.

The comparison of the main characteristics of female cases in the different periods revealed an abrupt increase in association with advertising not only for the occurrence of cases but also for the percentage of cases due to misunderstandings about the administration route, which was the main reason for exposure during the advertisement period. In the last 11 days of December, which fell within the period of the first advertising campaign, 100% of the female cases were exposed because of confusion over the administration route; this percentage was 81% when considering the entire *advertisement* period, whereas in the 5-year *pre-advertisement* period it was only 16% (Table 2). The television advertisement, which was discontinuously broadcast, emphasised the ability of women to achieve a quick remission of their "intimate problems" by simply going to a pharmacy and buying the product. During the first two campaigns, the advertisement did not contain any direct indication of the mode of use. In the third campaign, it included a written statement that the preparation was for topical-only use. However, this attempt at clarification did not seem to have any effect, given that 9 of the 11 cases observed during the last advertising campaign were exposed because of incorrect administration route, though there are too few cases to make a definitive conclusion. The percentage of women who misunderstood the correct mode of use decreased during the *post-advertisement* period, yet it remained higher than that in the *pre-advertisement* period, indicating that the misleading effect of the advertisement was long lasting.

A strength of this study was that it was based on routinely collected and readily available data and that during the study period the means of collecting data did not change. However, a potential

limitation of the study is that there may have been a selection bias in the population, which consisted of reports provided on a voluntary basis to the National PCCM. Nonetheless, the observed increase in the risk of exposure due to an incorrect administration route can hardly be explained by selection bias and can be reasonably considered to be indicative of an increased risk of this type of incident among users in the general population.

The reported findings document how DTCA can negatively affect the correct use of an OTC medication, highlighting the need for monitoring select outcomes, such as medication errors and adverse effects, before, during, and after advertising campaigns. Data routinely collected by PCCs, although referring to a select subset of cases of dangerous exposure and poisoning, can be useful in advertising surveillance and provide valuable information for regulatory agencies.

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Table 1. Mean daily rates and observed/expected ratios of ingestion of a BHC-containing gynaecological preparation reported to the National Poison Control Centre in Milan in 2005-2010

Period	Women						Men					
	Mean cases/day	**95%CI**	**Obs.**	**Exp.**	**O/E**	**95%CI**	**mean cases/day**	**95%CI**	**Obs.**	**Exp.**	**O/E**	**95%CI**
Pre-advertisement *Jan.1,2005-Dec.19,2009*	0.04	0.03-0.05	67	-	-	-	0.01	0.01-0.02	20	-	-	-
Advertisement *Dec.20,2009-Mar.6,2010*	0.83	0.64-1.06	64	8.55*	7.48	5.76-9.56	0.04	0.01-0.11	3	2.54*	1.18	0.24-3.45
Post-advertisement *Mar.7-Dec.31,2010*	0.19	0.14-0.24	56	18.87**	2.97	2.24-3.85	0.02	0.00-0.04	5	5.63**	0.89	0.29-2.07

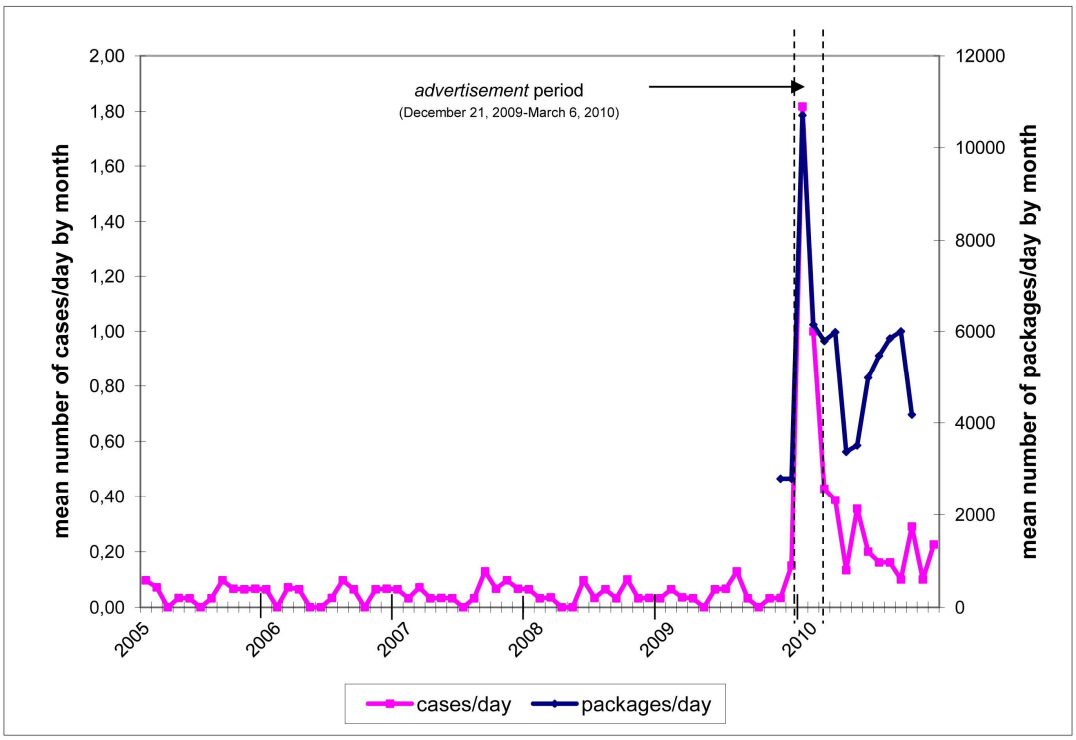
*Calculated adjusting for a 3.0-fold increase of the population at risk of exposure based on the ratio between the mean number of packages/day sold in the *advertisement* and *pre-advertisement* periods (8,381/2,791), respectively.
**Calculated adjusting for a 1.7-fold increase of the population at risk of exposure based on the ratio between the mean number of packages/day sold in the *post-* and *pre-advertisement* periods (4,764/2,791), respectively.

Table 2. Main characteristics of female cases of ingestion of a BHC-containing gynaecological preparation reported to the National Poison Control Centre in Milan in 2005-2010

	Period							
	Pre-advertisement (67 cases)		*Advertisement* (64 cases)			*Post-advertisement* (56 cases)		
	n.	**%**	**n.**	**%**	**P***	**n.**	**%**	**P***
All cases	**88**		**67**			**61**		
Women	**67**	**76.1**	**64**	**95.5**	0.001	**56**	**92.0**	0.025
Site of call for assistance					0.294			0.932
Hospital	28	41.8	33	51.6		24	42.9	
Private residence	24	35.8	15	23.4		21	37.5	
Other	15	22.4	16	25.0		11	19.6	
Age (years)					0.003			0.777
< 5	6	8.9	0	0.0		3	5.4	
5 – 19	14	20.9	4	6.2		9	16.1	
20 – 34	21	31.3	33	51.6		20	35.7	
35 – 49	10	14.9	16	25.0		12	21.4	
50 +	14	20.9	10	15.6		9	16.1	
Unknown	2	3.0	1	1.6		3	5.4	
Reason for exposure					<0.001			<0.001
Unintentional-general**	21	31.3	4	6.2		8	14.3	
Unintentional-medication error								
medicine exchange	35	52.2	8	12.5		17	30.4	
incorrect route	11	16.4	52	81.2		31	55.4	
Preparation								
500 mg granular form	65	97.0	60	93.8		47	83.9	
Others	1	2.3	3	4.7		9	16.1	
Unknown	1	1.1	1	1.6		0	0.0	
Medical outcomes					0.002			0.005
None	49	73.1	29	43.7		27	48.2	
At least one sign or symptom	18	26.9	35	54.6		29	51.8	
Minor	*17*	*25.4*	*31*	*48.4*		*22*	*39.3*	
Moderate	*1*	*1.5*	*4*	*6.2*		*7*	*12.5*	
Clinical effects								
Vertigo	6	8.9	12	18.7		8	14.3	
Oropharyngeal irritation	7	10.4	11	17.2		1	1.8	
Pyrosis	3	4.5	9	14.1		13	23.2	
Vomiting	5	7.5	5	7.8		9	16.1	
Nausea	3	4.5	7	10.9		4	7.1	
Pharyngeal pain	2	3.0	4	6.2		0	0.0	
Hallucinations	1	1.5	3	4.7		3	5.4	
Headache	0	0.0	4	6.2		2	3.6	
Other	6	8.9	9	13.4		12	21.4	

* Comparison with the *pre-advertisement* period using Pearsons' χ^2 test or Fisher's exact test; **Including cases who mistook BHC solution for drinking water or other beverages.

Figure 1. Distribution by year and month of the mean number of cases of ingestion of a BHC-containing gynaecological preparation reported to the National Poison Control Center in Milan in 2005-2010 and the mean number of packages/day sold in Italy between November 2009 and October 2010



Contributors: LS developed the research proposal, planned the study design and the analysis, and drafted and edited the paper. FD was responsible for data collection and assessment of severity of cases, and contributed to editing the paper. LL contributed to planning and performing the analyses and to drafting and editing the paper. MLC and FF contributed to editing the paper and are guarantors.

ORAL INGESTION OF A TOPICAL BENZYDAMINE-CONTAINING GYNAECOLOGICAL PREPARATION IN ASSOCIATION WITH TELEVISION ADVERTISING IN ITALY: ANALYSIS OF CASES MANAGED BY A NATIONAL POISON CONTROL CENTRE

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ORAL INGESTION OF A TOPICAL BENZYDAMINE HYDROCHLORIDE-CONTAINING GYNAECOLOGICAL PREPARATION IN ASSOCIATION WITH TELEVISION ADVERTISING IN ITALY: ANALYSIS OF CASES MANAGED BY A NATIONAL POISON CONTROL CENTRE

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ABSTRACT

Objective: To evaluate the impact of a television advertising campaign on the risk of oral ingestion of a topical non-prescription gynaecological preparation containing benzydamine hydrochloride.

Design: We analysed cases of exposure to the preparation reported to the National Poison Control Centre in Milan from January 2005 to December 2010. This period was divided into three separate periods: *pre-advertisement* (five years); *advertisement* (two and a half months); and *post-advertisement* (ten months). The periods were compared in terms of the observed/expected ratio of cases, with expected cases based on data from the *pre-advertisment* period and adjusted for variations in the number of users, estimated based on sales. The main characteristics of cases were compared for the three periods using Pearson's χ^2 test or Fisher's exact test.

Results: During the study period, 215 cases of ingestion of the preparation were reported. The adjusted observed/expected ratio of cases of ingestion in women was 7.48 (95% confidence interval: 5.76 to 9.56) in the *advertisement* period and 2.97 (95% CI: 2.24 to 3.85) in the *post-advertisement* period. Regarding the characteristics of cases, there was an increased proportion of cases of exposure due to confusion about the correct administration route in the *advertisement* and *post-advertisement* periods (81% and 55%, respectively, compared to 16% for the *pre-advertisement* period.) and of individuals with signs and symptoms related to exposure (55%, 52%, and 27%, respectively).

Conclusions: In Italy, an advertisement for a non-prescription medicine seems to have confused consumers regarding the adminstration route. This effect was observed even after the advertisement had stopped being broadcast. These results highlight the need for the monitoring of medication errors and adverse effects before, during, and after advertising.

ARTICLE SUMMARY

Article focus

The study is focused on documenting the impact of television advertising on the safe use of a benzydamine hydrochloride-containing gynaecological preparation in Italy.

Key messages

Advertising can affect the safe use of medicine. Select outcomes, such as medication errors, should be carefully monitored before, during, and after advertising campaigns. To this end, poison control centres can be extremely useful.

Strengths and limitations

The study is based on routinely collected and readily available data (i.e., reports and telephone calls made to a national poison control centre), which allowed for the comparison of the main characteristics of cases of dangerous exposure to a medicine and for the evaluation of the association between the occurrence of cases and a television advertising campaign. The main potential limitation is that the data were provided on a voluntary basis to the poison control centre, so that they may not be representative of all cases occurring in the general population.

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Competing interest

All authors have completed the Unified Competing Interest form at www.icmje.org/coi-disclousure.pdf (available on request from the corresponding author) and declare that all authors had: (1) No financial support for the submitted work as declared above; (2) No financial relationships with commercial entities that might have an interest in the submitted work; (3) No spouses, partners, or children with relationships with commercial entities that might have an interest in the submitted work; (4) No non-financial interests that may be relevant to the submitted work.

Introduction

Benzydamine hydrochloride (BHC) (CAS no. 132-69-4) is a local anti-inflammatory and analgesic active ingredient first synthesised by the Angelini research laboratories in the mid-1960s. Since then, topical preparations containing BHC have been marketed worldwide for the symptomatic treatment of oropharyngeal and gynaecological conditions (1). These preparations are sold as concentrated or ready-to-use solutions or as a powder to be dissolved in water. Topical preparations of BHC are usually well tolerated, with infrequent side-effects (2). Absorption through the skin and mucosa is low, whereas experimental data indicate that BHC is rapidly absorbed in the gastrointestinal tract (3,4). A limited number of reports on acute oral exposure in humans have shown that BHC overdose can cause nausea, vomiting, visual hallucinations, oesophageal irritation, agitation and somnolence (5-8). These effects have resulted mainly from the ingestion of gynaecological preparations because of confusion about the correct administration route and the preparations' being mistaken for oral medicines (8). A few cases of injuries due to intentional ingestion for recreational use have also been reported (7,9).

In Italy, from 1977 to 2009, BHC-containing gynaecological preparations manufactured by Angelini were classified as pharmacy-supervised drugs (sold under the supervision of a pharmacy), a category of non-prescription drugs for which advertising to the public is prohibited. In April 2009, these preparations were reclassified as over-the-counter (OTC) drugs with the following therapeutic indications: vulvovaginitis of any origin or nature, characterised by small vaginal discharge, itching, irritation, burning, and vulvar pain; and personal hygiene during puerperium. The label on the package was changed from "vaginal solution" to "cutaneus solution for external genital organs" (10). Given the drug's new status, advertising to the public was allowed, and the manufacturer launched an intensive television advertising campaign between December 20, 2009 and January 2, 2010, followed by a second campaign between January 17 and 23, 2010. The advertisement focused on solidarity among women and on their ability to solve their "intimate problems" by using the

advertised preparation. At the end of the advertisement, an allusion was made to the mode of use, with a woman's silhouette with concentric circles on the abdomen.

During the first television campaign, the National Poison Control Centre in Milan (PCCM) observed an unexpectedly increased number of requests for assistance for cases of unintentional oral ingestion (i.e., from approximately 1 case per month to 2 cases per day). Based on these findings, the Italian Ministry of Health required that the advertisement be revised to clarify that the product was for topical use. The advertisement was rebroadcast between February 21 and 27, 2010, with a written statement at the end of the advertisement stating that the preparation was for topical use only and a woman's silhouette with concentric circles on the pubis area. Afterwards, the advertisement was voluntarily stopped by the manufacturer. The objective of the present study was to document how unintentional oral exposure to BHC-containing gynaecological preparations was inadvertently promoted by television advertising in Italy.

Materials and methods

Each year the PCCM receives approximately 42,000 reports of human exposure to different types of substances (11), accounting for more than 60% of all cases referred to Italian PCCs (12). The PCCM mainly provides consultation to hospitals (60% of cases) and to the general public (30% of cases) throughout Italy. Assistance for diagnosing and treating poisonings is provided by medical toxicologists, mainly over the phone. For each case, the toxicologist collects the following data in real-time using a standard form: demographic characteristics; exposure characteristics (e.g., substance/commercial product, route of exposure, reason for exposure, dose, and latency between exposure and onset of clinical effects); signs and symptoms; therapy; and outcome. About 45% of the human exposures managed by PCCM are medicine-related; of these, about 17% of these individuals are victims of the inappropriate use of medication (13).

For the present study, the PCCM database was searched from January 1, 2005 to December 31, 2010 to identify all cases of inappropriate exposure to the BHC-containing gynaecological preparation, which is available in diverse forms (i.e., concentrated solution, ready-to-use solution, and powder). A clinical toxicologist (FD) reviewed the available information for data consistency and to grade the severity of outcome according to the Poisoning Severity Score (i.e., *none*, no signs/symptoms; *minor*, mild, transient, and spontaneously resolving signs/symptoms; *moderate*, pronounced or prolonged signs/symptoms; *severe*, life-threatening signs/symptoms or resulting in significant residual disability or disfigurement; *fatal*, death as a result of exposure or of direct complications of the exposure effects) (14). For the purposes of the present analysis, the identified cases were classified into three groups based on exposure period: i) the *pre-advertisement* period (i.e., from January 1, 2005 to December 19, 2009), before the advertisement was broadcast; ii) the *advertisement* period (i.e., from December 20, 2009 to February 27, 2010), when the advertisement was repeatedly launched, plus the week following the last day of broadcast (i.e., from February 28

to March 6, 2010), assuming that the advertisement still had an effect; and iii) the *post-advertisement period* (i.e., from March 7 to December 31, 2010).

The mean number of packages sold per day during these periods was estimated based on the information provided by the manufacturer on the number of packages sold per month from November 2009 to October 2010 (). We assumed that the sales during the *pre-advertisement* period remained constant; we thus decided to calculate the mean number of packages sold per day based on sales in November 2009 (n=83,745, corresponding to 2,791 packages/day). Since the first 20 days of December were included in the *pre-advertisement* period, the quantity assumed to be sold in these 20 days (55,820 packages) was based on the estimated daily sales in November 2009. This quantity was subtracted from the total number of packages sold in December (n=173,724). The remaining quantity (117,904 packages) was used to estimate the mean number of packages/day sold in the period December 21-31 (n=10,718) under the assumption that the observed increase was completely driven by advertising. During the entire *advertisement* period, an estimated mean of 8,381 packages/day were sold, whereas in the *post-advertisement* period a mean of 4,764 packages/day were estimated to be sold. The ratio of *advertisement*-period sales to *pre-advertisement* sales and the ratio of *post-advertisement* sales to *pre-advertisement* sales were calculated as an indicator of the increased number of users (i.e., the population at risk of exposure). These ratios corresponded to a 3.0-fold mean increase in the *advertisement* period (range, by calendar month: 2.1 to 3.8) and a 1.7-fold mean increase in the *post-advertisement* period (range, 1.2 to 2.1).

The mean daily rate (i.e., the mean number of cases of exposure/day) by gender and period was calculated, as were the 95% confidence intervals (95% CI), assuming a Poisson's process. In the *pre-advertisement* period, the mean daily rate for both men and women was assumed to be constant over time and used to estimate the expected number of cases in the *advertisement* and *post-advertisement* periods. These expected values were adjusted by the estimated increases in the population at risk of exposure in the two periods. The ratio of observed to adjusted expected cases

(O/E) was used as a measure of the association between inappropriate exposure and television advertising. The 95% CIs of the O/E ratio were derived assuming a Poisson's process for the observed cases (15). The main characteristics of cases in the three periods were compared using Pearson's χ^2 test or Fisher's exact test.

Results

A total of 215 cases of oral exposure to the advertised gynaecological preparations were identified. Of these, 187 were women and 28 were men. All cases were unintentionally exposed through oral ingestion, with the exception of one man who intentionally ingested the preparation.

The mean number of cases/day observed by month in the three different periods is shown in Figure 1; the mean number of packages sold per day is also shown. In the *pre-advertisement* period, there were 15-20 cases/year and 0-4 cases/month. The mean number of cases/day by month ranged from 0.00 to 0.15. In the *advertisement* period, 1.85 cases/day were observed during the last 10 days of December, which were completely covered by the first advertising campaign. In January, 1.00 cases/day were observed; the beginning of this month was covered by the first advertising campaign, which was broadcast until January 2nd, and, subsequently, from January 17th to 23rd by the second advertising campaign. In February, 0.48 cases/day were observed; the third advertising campaign was broadcast from February 23rd to 27th. The estimated number of packages sold per day varied from 10,718 in the last ten days of December, to 6,142 in January, and 5,788 in February. During the *post-advertisement* period (i.e., from March 7 to December 31, 2010), the mean number of cases/day ranged from 0.10 to 0.35. The estimated number of packages sold per day ranged from 6,000 to 3,373.

The distribution of cases by gender and period and the corresponding daily rates are shown in Table 1. The observed/expected ratios, adjusted by the estimated increase in the population at risk of exposure (i.e., 3.0- and 1.7-fold increase in the *advertisement* and *post-advertisement* period, respectively) are also shown. In the *pre-advertisement* period, 67 cases occurred in women, accounting for 0.04 cases/day (95% CI, 0.03 to 0.05) and 20 cases occurred in men (0.01 cases/day, 95% CI 0.01 to 0.02). In the *advertisement* period, in women, there were 64 observed cases and 8.55 expected cases (O/E 7.48, 95% CI, 5.76-9.56), whereas in men the observed cases were close to the expected ones (3 *vs.* 2.54, O/E 1.18, 95% CI, 0.24-3.45). In the *post-advertisement* period, in

women, there were 56 observed cases and 18.87 expected cases (O/E 2.97, 2.24 to 3.85). In men, there were 5 observed cases and 5.63 expected cases (O/E 0.89, 0.29 to 2.07).

The main characteristics of female cases by period of exposure are reported in Table 2. In the *advertisement* and *post-advertisement* periods, the percentage of females (95 and 92%, respectively) was significantly higher than that in the *pre-advertisement* period (76%, P=0.001 and 0.025, respectively). The percentage of individuals who were hospitalised in the *advertisement* period (52%) was slightly higher, though not significantly, than that in the *pre-advertisement* (42%) and *post-advertisement* (43%) periods. When comparing cases in the *pre-advertisement* and *advertisement* periods, significantly different distributions were found for age class (P=0.003), reason for exposure (P<0.001), and medical outcome (P=0.002). In particular, the *advertisement* period, compared to the *pre-advertisement* period, was characterized by a predominance of cases aged 20-49 years (77% *v* 46%), medication error due to misunderstanding of the correct mode of use (81% *v* 16%), and individuals suffering recognized BHC-related effects (55% *v* 27%). In the *post-advertisement* period, the distribution of cases by age was comparable to that reported in the *pre-advertisement* period, whereas significant differences were found for the distribution of cases by reason of exposure (P<0.001) and medical outcomes (P=0.005).

Altogether, 82 women suffered recognized BHC-related effects. The severity of medical outcomes was minor in 70 women (85%), and moderate in 12 (13%). No severe or fatal effects were observed. The signs and symptoms most frequently associated with BHC ingestion included: vertigo (n=26), oropharyngeal irritation (n=19), pyrosis (n=25), vomiting (n=19), nausea (n=14), pharyngeal pain (n=6), hallucinations (n=7), and headache (n=6) (Table 2).

With reference to men exposed in the *pre-advertisement* period (n=20), 50% mistook a BHC solution for drinking water or other beverage, whereas for the remaining 50% the exposure was due to confusion with other medicine. Similarly, in the *advertisement* period, two cases reported having mistook a BHC solution for a beverage and one for another medicine. Among the five cases detected in the *post-advertisement* period, in one case the exposure was due to intentional abuse;

one case each mistook the solution for a beverage or another medicine. Altogether, 6 patients were symptomatic and suffered oropharyngeal irritation (n=3) and vomiting (n=3).

Comments

In the European Community, advertising to the public is only allowed for medicinal products that are classified as "not subject to medical prescription" (16), commonly referred to as "OTC". This classification should be based on an evaluation of the balance between the potential benefits of the product's being readily available for self-treatment and the potential harm resulting from unsupervised or inappropriate use. Thus the safety of OTC medicines needs to be continuously monitored, to identify unforeseen problems and implement suitable interventions to minimise the potential for harm (17-19).

Advertising to the public is a source of information that tends to emphasise the beneficial effects of the advertised product (20), which could inadvertently contribute to unnecessary or inappropriate use. However, the impact of advertising to the public on the safe use of non-prescription medicines has only been studied to a limited extent (21,22).

Some studies have shown that self-medication of vaginal conditions with OTC antifungal preparations is associated with unnecessary use and a delay in proper diagnosis and treatment (23,24). With specific regard to BHC-containing gynaecological preparations, a study in Spain has shown a high frequency of medication error due to misunderstandings about the correct administration route (8).

In Italy, until April 2009, BHC-containing gynaecological preparations had been classified in a category of medicines that can be obtained without a prescription yet for which advertising to the public is not allowed. The re-classification as "OTC" was not associated *per se* with an increase in cases of exposure (Figure 1) or with changes in the case distribution by gender or other characteristics. Instead, the daily rate of cases of exposure reported to the National PCCM increased abruptly in association with television advertising, and this increase can be explained only in part by the increased number of users. In particular, during the first advertising campaign (i.e., December 20, 2009 - January 2, 2010), there was a 17.5-fold increase in the daily rate of cases of oral

exposure compared to the *pre-advertisement* period, but only a 3.8-fold increase in the number of users; when adjusting for the number of users, there was still a 9.5-fold increase in the daily rate of cases. The analysis of the observed/expected ratio, which was performed taking into account a mean 3.0-fold increase in the number of users during the *advertisement* period, showed a statistically significant 7.5-fold increase in the risk of exposure in association with advertising. In the *post-advertisement*-period, when the estimated number of users was on average 1.7-fold higher than that in the *pre-advertisement* period, the risk of exposure was approximately 3 times higher than that in the *pre-advertisement* period, suggesting that the advertisement had a long-lasting effect.

The comparison of the main characteristics of female cases in the different periods revealed an abrupt increase in association with advertising not only for the occurrence of cases but also for the percentage of cases due to misunderstandings about the administration route, which was the main reason for exposure during the advertisement period. In the last 11 days of December, which fell within the period of the first advertising campaign, 100% of the female cases were exposed because of confusion over the administration route; this percentage was 81% when considering the entire *advertisement* period, whereas in the 5-year *pre-advertisement* period it was only 16% (Table 2). The television advertisement, which was discontinuously broadcast, emphasised the ability of women to achieve a quick remission of their "intimate problems" by simply going to a pharmacy and buying the product. During the first two campaigns, the advertisement did not contain any direct indication of the mode of use. In the third campaign, it included a written statement that the preparation was for topical-only use. However, this attempt at clarification did not seem to have any effect, given that 9 of the 11 cases observed during the last advertising campaign were exposed because of incorrect administration route, though there are too few cases to make a definitive conclusion. The percentage of women who misunderstood the correct mode of use decreased during the *post-advertisement* period, yet it remained higher than that in the *pre-advertisement* period, indicating that the misleading effect of the advertisement was long lasting.

A strength of this study was that it was based on routinely collected and readily available data and that during the study period the means of collecting data did not change. However, a potential limitation of the study is that there may have been a selection bias in the population, which consisted of reports provided on a voluntary basis to the National PCCM. Nonetheless, the observed increase in the risk of exposure due to an incorrect administration route can hardly be explained by selection bias and can be reasonably considered to be indicative of an increased risk of this type of incident among users in the general population.

The reported findings document how advertising to the public can negatively affect the correct use of an OTC medication, highlighting the need for monitoring select outcomes, such as medication errors and adverse effects, before, during, and after advertising campaigns. Data routinely collected by PCCs, although referring to a select subset of cases of dangerous exposure and poisoning, can be useful in advertising surveillance and provide valuable information for regulatory agencies.

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Table 1. Mean daily rates and observed/expected ratios of ingestion of a BHC-containing gynaecological preparation reported to the National Poison Control Centre in Milan in 2005-2010

Period	Women						Men					
	Mean cases/day	95%CI	Obs.	Exp.	O/E	95%CI	mean cases/day	95%CI	Obs.	Exp.	O/E	95%CI
Pre-advertisement *Jan.1,2005-Dec.19,2009*	0.04	0.03-0.05	67	-	-	-	0.01	0.01-0.02	20	-	-	-
Advertisement *Dec.20,2009-Mar.6,2010*	0.83	0.64-1.06	64	8.55*	7.48	5.76-9.56	0.04	0.01-0.11	3	2.54*	1.18	0.24-3.45
Post-advertisement *Mar.7-Dec.31,2010*	0.19	0.14-0.24	56	18.87**	2.97	2.24-3.85	0.02	0.00-0.04	5	5.63**	0.89	0.29-2.07

*Calculated adjusting for a 3.0-fold increase of the population at risk of exposure based on the ratio between the mean number of packages/day sold in the *advertisement* and *pre-advertisement* periods (8,381/2,791), respectively.
**Calculated adjusting for a 1.7-fold increase of the population at risk of exposure based on the ratio between the mean number of packages/day sold in the *post-* and *pre-advertisement* periods (4,764/2,791), respectively.

Table 2. Main characteristics of female cases of ingestion of a BHC-containing gynaecological preparation reported to the National Poison Control Centre in Milan in 2005-2010

	Period							
	Pre-advertisement (67 cases)		*Advertisement* (64 cases)			*Post-advertisement* (56 cases)		
	n.	**%**	**n.**	**%**	**P***	**n.**	**%**	**P***
All cases	**88**		**67**			**61**		
Women	**67**	**76.1**	**64**	**95.5**	0.001	**56**	**92.0**	0.025
Site of call for assistance					0.294			0.932
Hospital	28	41.8	33	51.6		24	42.9	
Private residence	24	35.8	15	23.4		21	37.5	
Other	15	22.4	16	25.0		11	19.6	
Age (years)					0.003			0.777
< 5	6	8.9	0	0.0		3	5.4	
5 – 19	14	20.9	4	6.2		9	16.1	
20 – 34	21	31.3	33	51.6		20	35.7	
35 – 49	10	14.9	16	25.0		12	21.4	
50 +	14	20.9	10	15.6		9	16.1	
Unknown	2	3.0	1	1.6		3	5.4	
Reason for exposure					<0.001			<0.001
Unintentional-general**	21	31.3	4	6.2		8	14.3	
Unintentional-medication error								
medicine exchange	35	52.2	8	12.5		17	30.4	
incorrect route	11	16.4	52	81.2		31	55.4	
Preparation								
500 mg granular form	65	97.0	60	93.8		47	83.9	
Others	1	2.3	3	4.7		9	16.1	
Unknown	1	1.1	1	1.6		0	0.0	
Medical outcomes					0.002			0.005
None	49	73.1	29	43.7		27	48.2	
At least one sign or symptom	18	26.9	35	54.6		29	51.8	
Minor	*17*	*25.4*	*31*	*48.4*		*22*	*39.3*	
Moderate	*1*	*1.5*	*4*	*6.2*		*7*	*12.5*	
Clinical effects								
Vertigo	6	8.9	12	18.7		8	14.3	
Oropharyngeal irritation	7	10.4	11	17.2		1	1.8	
Pyrosis	3	4.5	9	14.1		13	23.2	
Vomiting	5	7.5	5	7.8		9	16.1	
Nausea	3	4.5	7	10.9		4	7.1	
Pharyngeal pain	2	3.0	4	6.2		0	0.0	
Hallucinations	1	1.5	3	4.7		3	5.4	
Headache	0	0.0	4	6.2		2	3.6	
Other	6	8.9	9	13.4		12	21.4	

* Comparison with the *pre-advertisement* period using Pearsons' χ^2 test or Fisher's exact test; **Including cases who mistook BHC solution for drinking water or other beverages.

Contributors: LS developed the research proposal, planned the study design and the analysis, and drafted and edited the paper. FD was responsible for data collection and assessment of severity of cases, and contributed to editing the paper. LL contributed to planning and performing the analyses and to drafting and editing the paper. MLC and FF contributed to editing the paper and are guarantors.

Checklist of items included in the study

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Figure 1. Distribution by year and month of the mean number of cases of ingestion of a BHC-containing gynaecological preparation reported to the National Poison Control Center in Milan in 2005-2010 and the mean number of packages/day sold in Italy between November 2009 and October 2010