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Efficacies of Regulatory Policies to Control Massive Use of Diphenoxylate

[1]Amir Farshchi, [1]Mona Jaberidoost, [1]Akbar Abdollahiasl and [1,2]Mohammad Abdollahi
[1]Department of Pharmacoeconomics and Pharmaceutical Administration, Faculty of Pharmacy,
Tehran University of Medical Sciences, Tehran, Iran
[2]Department of Toxicology and Pharmacology, Faculty of Pharmacy,
Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran

Abstract: Iran has been one of the highest users of diphenoxylate in the world in 2008. Iranian food and drug organisation (FDO) established some rules to control the usage of this drug included rationalizing the supply and doubling the price. Data were gathered from the distributors and wholesalers of this medicine in the country during 2006-2010. These data were cross-checked with importation data in the Ministry of Health and a trend analysis was tabulated. In 2009, the average consumption reached to less than 650 million tablets which show 42% decrease in comparison to the previous year. After the second intervention, there has been no significant change in the trend. The first intervention has controlled the use of diphenoxylate by reduction of market need and lessening diphenoxylate unauthorized use. Data do not support the efficiency of second intervention meaning that doubling the price does not work.

Key words: Abuse, cost, diphenoxylate, toxicity, utilization, Iran

INTRODUCTION

To have a secure pharmaceutical market an effective strategy is needed to recognize all health indicators such as exact rates of diseases and adverse drug reactions, demands, resources and opportunities (Abdollahiasl *et al*., 2011a) but unfortunately, the system, structures and mechanisms for control of drugs in Iran, although is in place but they do not function properly in some topics (Nikfar *et al*., 2005). Diphenoxylate is a synthetic derivate of pethidine that is mainly used in supportive management of acute and chronic diarrhea. Because of opioid-like effects, diphenoxylate is a choice of abuse and it is listed in Schedule III of the 1961 Convention (Katzung, 2011). Based on United Nation reports, China and India are the main producers and also users of diphenoxylate in the world. Iran is the top importer and the third user of diphenoxylate in the world. Iran imported 2 of 16 tons (17%) of total diphenoxylate produced in 2007 (United Nations, 2009). The question is why a country with 1% of the world population could consume about 17% of the whole production of diphenoxylate in the world. The Iranian Food and Drug Organisation (FDO) as the main responsible body for rationalizing drug use established some rules to limit the usage rate (Soleymani *et al*., 2009). Despite diphenoxylate is a prescription drug but some estimations indicates that only less than 5% is used by prescriptions and the main use seems misusage by addicts or any unknown reason. One of the reasons behind this extreme use of diphenoxylate is its low price that makes it affordable for most of abusers and meanwhile lead to a competitive mass production by various pharmaceutical companies to compensate demand of pharmacies. The same trend of misuse was already confirmed for antibiotics in Iran (Abdollahiasl *et al*., 2011b). Compatible with data from use of diphenoxylate, our recent study indicated that naloxone as an antidote of diphenoxylate and other opioids is produced in high amounts in Iran to provide requirements of poisoning centers (Nikfar *et al*., 2011). To solve this problem immediately, FDO tried to control import of the active ingredient followed by more control on distributors and pharmacies (Dinarvand, 2009). The other policy was doubling the user price that became effective in the middle of 2009. This study aimed to show the effectiveness of these two interventions by evaluating monthly use of diphenoxylate.

MATERIALS AND METHODS

The monthly production and sale of this medicine were requested from the six manufacturers and 15 distributors around the country. Although, the request letters were sent by the Narcotic Control Office of FDO to

Corresponding Author: Mohammad Abdollahi, Department of Toxicology and Pharmacology, Faculty of Pharmacy, Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran

guarantee receiving a true answer, data were cross-checked with raw material importation data within FDO. A time-trend analysis was done on summarized tabulated data. DDD (defined daily dose) and DID (DDD per 1000 inhabitant patient per day) were calculated by the following formula:

- DDD = Defined daily doses used by a thousand of population in a day
- DID = Annual sale multiplied by DDD and 1000 divided by (strength of drug multiplied by population and 365):

Therefore, the monthly data were calculated as follows:

- DID = (monthly sale multiplied by DDD and 1000) divided by (strength of drug multiplied by population and 30)

RESULTS AND DISCUSSION

There are some variations in monthly use of diphenoxylate but annual data show that 0.786, 1.215, 1.044 and 0.610 billion tablets of diphenoxylate 2.5 mg were sold in 2006, 2007, 2008 and 2009, respectively (Fig. 1). For adjusting the monthly sales data, the average sale of three months including a month before and a month after of each considered as that month sale. This kind of moving average could decline some sharp differences in monthly sale and smooth the chart (Fig. 2). For removing the effect of population growth, data changed to DDD/1000 inhabitants/day (DID). Usually, calculation of DID is based on annual data. Both annual and monthly data were considered (Fig. 3). Figure 4 illustrates the exact monthly changes that is adjusted by moving average trend and compared to unit price of diphenoxylate 2.5 mg tablet.

The monthly sale is a surrogate for use of drug while a gap between the amounts of diphenoxylate bought by pharmacies and the amounts used is clear. This can be explained by pharmacies' stocks level and the leftovers drugs in houses. In this study, trend of sale was obtained and we could not find any reason for considerable changing of these factors during the study. The annual sale shows an increasing trend until 2007 where a small decline occurred in 2008 and a major reduction happened in 2009 (Fig. 1). Two kinds of up and down in the trend is obvious. The small changes seem usual and can be explained by usual errors in distribution system, work calendar, transportation lag time and the cash flow between producers and distributors. By applying a three-month moving average (putting the average sales of each tree months instead of the middle month and moving this pattern for all months), the trend was smoothed (Fig. 2). Interpretation of major up and down needs full information about the interventions, events and policies happened during the examined period. The highest sale happened in the third season of 2007 (more than 120 million tablets per month) and a major decline after that continued to the first season of 2008 that was because of saturation of pharmacies' stocks but it went up again in middle of 2008. In the third season of 2008, after the first intervention, a gradual decline was started and continued up to end of 2009 and reached to a plateau in the last 6 months. The first intervention was started by controlling the imported active ingredient through official power of FDO. This intervention was supported by a warning letter sent to all distributors describing the undergoing inspection for any unauthorized use of diphenoxylate.

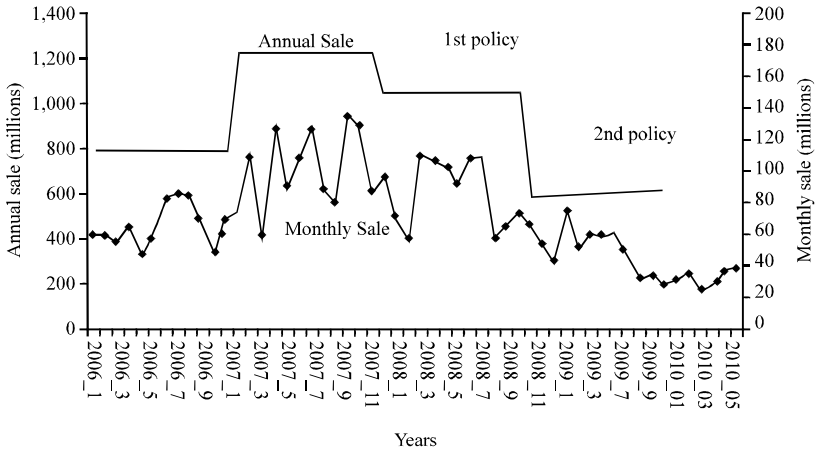

Fig. 1: Annual and monthly sales of diphenoxylate 2.5 mg tablets in Iran during 2006-2010

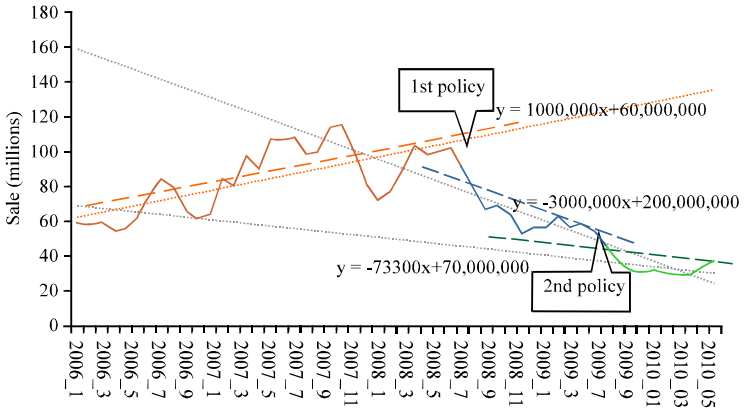

Fig. 2: Three months moving average sales of diphenoxylate 2.5 mg tablets in Iran during 2006-2010

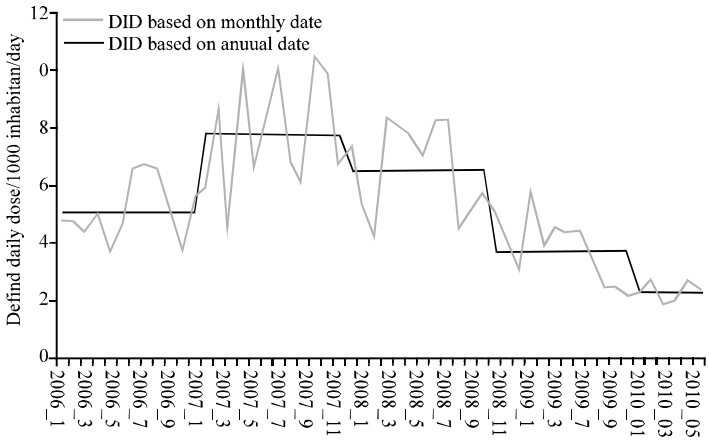

Fig. 3: Defined daily dose/1000 inhabitants/day of diphenoxylate 2.5 mg tablets in Iran during 2006-2010

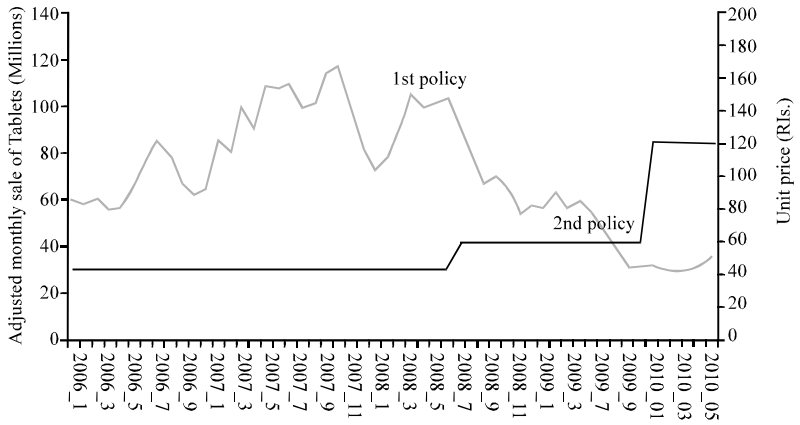

Fig. 4: Adjusted monthly sales against unit price of diphenoxylate 2.5 mg tablets in Iran during 2006-2010

FDO believed that this policy could control behavior of manufacturers of diphenoxylate but meanwhile they believed that the policy could not be effective for market demand. Since, a big difference between anti-diarrhea dose and opiate-like dose exists, the abusers of this drug have learned to use many tablets. Then the FDO decided

to make it unaffordable for abusers by serious warning of pharmacies. The price of each tablet of diphenoxylate was 43 Iranian Rials (IRR) equal to 0.0043 US Dollar (USD) till the first season of 2008 when it had a small increase because of usual inflation rate and reached 60 IRR equal to 0.006 USD. Then FDO decided to a marked increasing the price of some drugs that might be abused. The offered price for diphenoxylate changed to 1000 IRR equal to 0.1 USD per tablet and the producers were asked to return the margin to the FDO. According to rules, this kind of cash flow must get parliament approval. The parliament agreed to just double the price. Although, FDO believed that doubling the price could not affect the affordability of this drug (120 IRR = 0.012 USD) but FDO was obliged to apply it in the last months of 2009. But the results did not show any significant change in the existing trend (Fig. 4) confirming unhelpfulness of the rule for the purpose of drug usage control. If the study period is divided into three parts including before the first policy, between two policies and after the second policy to check the correlations, a positive slop is evident that means an increase in the sale. After the first intervention, the trend significantly went down and the slope became negative. After the second intervention, the slope was still negative but its absolute value was reduced. This means that after the second policy became effective, not only the trend did not decrease but also it reached a plateau phase (Fig. 2). For eliminating the effect of population growth on the trend, data changed to the index named DID that has been defined by WHO collaborating center for drug statistics methodology. As shown in Fig. 3, the sale on the basis of DID has the same trend indicating that population growth has no significant effect on the sale of diphenoxylate.

Taken collectively, limiting the supply of diphenoxylate and warning to the distributors controlled the abuse of diphenoxylate. But this plan to decrease affordability has no effect on the trend and it has only increased workload of narcotic office in the MOH (Niens *et al*., 2010). At the end of period it sounds that the trend reaches a plateau and thus some other interventions are needed to rationalize the use. A significant tax mark-up on the price, promoting loperamide as a therapeutic substitute, penalizing pharmacies which do not observe the (Over-the counter markets) OTC rules and promoting the other legal methods for treating addicts are some policies that should be followed.

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