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## Cost and Utilization Study of Antidotes: An Iranian Experience

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**Abstract:** Epidemiological data show that the most inpatient disease resulting in hospitalization in Iran is poisoning where drug poisoning is the second cause of mortality in hospitalized patients. There is no report on the use, availability and cost expenditure of antidotes in the country. Regarding the importance of this kind of information in health policy, we aimed to review accessibility and affordability of antidotes in Iran as a sample model. Demographic and epidemiologic data about antidotes and their impacts in economic situation of the country during 2004-2008 were extracted from Iranian drug affair's, drug selection committee, pharmaceuticals statistics, direct interview with stockholders and key opinion leaders in toxicology and World Health Organization (WHO) reports. Data were extracted and analyzed for demographic, economic and health information, availability and accessibility of antidotes and five-year cost-utilization trends of antidotes. As a developing country, Gross National Production (GNP) per capita in Iran is about 7000 \$US. Gross national income per capita in Iran is 9,800 USA dollar (USD). Total expenditure on health per capita is 731 USD that is 7.8% of Gross Domestic Production (GDP) and total drug expenditure is 24000 billion Rials (10000 Rials≈1 USD). Iranian drug list (IDL) include most of antidotes, while 73% of them are registered and available in the market. Entire IDL includes 2230 medicines that 27 of them are antidote (1.1%). The volume of utilization of existing antidotes during 5 years indicate that 25% of them are almost expensive (more than 40000 Rials or 10 dollars) that is 1% of expenditure basket of Iran. All antidotes are under umbrella of insurance. Because of multi-purpose use of these drugs and high price of some of them, a real estimation of demand for good management of poisoning and pharmaceutical regulation and supply management is necessary for having a strategic depot. More feasible and reliable procurements, appropriate information and effective integration of health care services would have a good impact on poisoning management and policy making to better afford health cares in all countries like Iran. Effective impact of poisoning in economical and social concerns of the life necessitates implementation of stronger policies in clinical toxicology matters.

**Key words:** Antidotes, drug affair's, pharmaceutical regulation, clinical toxicology, pharmacoeconomics

### INTRODUCTION

Epidemiological data show that the most inpatient disease in Iran resulting in hospitalization is poisoning. In addition, drug poisoning is the second cause of mortality in hospitalized patients in the country (Anonymous, 2008). For management of most of poisonings, at least one kind of antidote should be used. Antidote is a natural or synthetic compound that interacts with the action of toxin in the body. Until now, more than 30 antidotes in different

categories have been known in the world (<http://inchem.org>, September 2009; Theakston *et al.*, 2003; Abdollahi *et al.*, 2003).

Iran like other countries faces many cases of human drug overdose and poisoning that need special poisoning care and existence of specific antidotes (Ghazinour *et al.*, 2009; Shadnia *et al.*, 2007; Moghadamnia and Abdollahi, 2002; Abdollahi *et al.*, 1997). As reported earlier, Iran has one of high-standard drug registration policies in the region that one of its main objectives is to afford essential

drugs such as antidotes available for treatment and management of diseases within the country (Nikfar *et al.*, 2005) and review of Iranian data would be a sample model for future studies specially in neighbor countries.

Assessment of accessibility and utilization of antidotes has a great impact for policy-makers because procurement of them is costly for government and it is very important to evaluate them in terms of availability, accessibility, affordability and their rationality of use.

There is no report on the use, availability and cost expenditure of antidotes in the country yet. Regarding the importance of this kind of information in health policy, we aimed to systematically review accessibility and affordability of antidotes in Iran during 2004-2008.

### MATERIALS AND METHODS

Demographic and epidemiologic data about antidotes and their impacts in economic situation of the country were extracted from Iranian drug affair's, drug selection committee, pharmaceuticals statistics, direct interview with stockholders and key opinion leaders in toxicology and World Health Organization (WHO) reports (<http://www.emro.who.int> access date: September 2009).

Data were extracted and analysed in 3 different manners including demographic, economic and health information, availability and accessibility of antidotes and 5 year cost-utilization trends.

For evaluation of availability, Iranian drug list was evaluated for existence of antidotes in the country. Information of registered drugs and their prices were collected from Iranian pharmaceutical regulatory affairs for evaluation of accessibility and affordability.

### RESULTS

#### Demographic, economic and health information:

Background information about demographic, economic and health contexts in 2006 have been summarized in Table 1. As shown in this Table 1, the population of Iran is more than 70,270,000 and the life expectancy for male and female are 69 and 73 years, respectively. Gross national income per capita in Iran is 9,800 USA dollar (USD).

Total expenditure on health per capita is 731 USD that is 7.8% of GDP (Gross Domestic Production) and total drug expenditure is 24000 billion Rials (10000 Rials≈1 USD). Data in this table show that probability of dying under age five is 35 per 1000 live births. Meanwhile probability of dying between age of 15 and 60 years for males and females were 170 and 106 per 1000 population, respectively.

Table 1: Demographic, economic and health information in Iran

No.	Economical and health information	Value
1	Total population	70,270,000
2	Gross national income per capita (PPP international \$)	9,800
3	Life expectancy at birth for male (year)	69
4	Life expectancy at birth for female (year)	73
5	Probability of dying under five (per 1 000 live births)	35
6	Probability of dying between 15 and 60 years for male (per 1,000 population)	170
7	Probability of dying between 15 and 60 years for female (per 1,000 population)	106
8	Total expenditure on health per capita (Intl \$, 2006)	731
9	Total expenditure on health as % of GDP (2006)	7.8

Table 2: Availability and accessibility of antidotes in Iranian drug list and in the market

No.	Name of antidotes	Available in IDL	Available in the market
1	Acetylcysteine	Yes	Yes
2	Anyl nitrite	Yes	Yes
3	Antibotulism polyvalent	Yes	Yes
4	Antiscorpion venom serum	Yes	Yes
5	Antisnake venom serum	Yes	Yes
6	Atropine sulfate	Yes	Yes
7	Benzpropine Mesylate	Yes	No
8	Calcium disodium edetate (EDTA)	Yes	No
9	Deferoxamine Mesylate	Yes	Yes
10	Dimercaprol (BAL)	Yes	Yes
11	Diphenhydramine hydrochloride	No	No
12	Ethanol	Yes	No
13	Flumazenil	Yes	Yes
14	Fomepizole	Yes	No
15	Fragment antigen binding (Fab)	Yes	No
16	Glucagon	Yes	Yes
17	Mesoxalic acid	No	No
18	Methylene blue	Yes	Yes
19	Naloxone hydrochloride	Yes	Yes
20	Oxygen	Yes	Yes
21	Penicillamine	Yes	Yes
22	Physostigmine sulfate	Yes	No
23	Pralidoxime chloride	Yes	Yes
24	Protamine sulfate	Yes	Yes
25	Prussian blue	No	No
26	Pyridoxine	Yes	Yes
27	Sodium nitrite	Yes	Yes
28	Succimer	Yes	Yes
29	Thiosulfate sodium	Yes	Yes
30	Vitamin K	Yes	Yes

**Availability and accessibility of antidotes:** Table 2 shows the list of antidotes and their availability in IDL. In addition, the registered antidotes which are accessible in the market are shown in Table 2. As seen, different processes are needed to add a new drug to national drug list and for registration. Registration means that drug is accessible in the pharmacies. Ninety percent of all antidotes are available in IDL while 73% of them are registered and available in the market. Entire IDL includes 2230 medicines that 27 of them are antidote (1.1%).

**Five year utilization trends of antidotes:** Five-year utilization trends of antidotes in Iran including the amount of use in each year and the price of each antidote are

Table 3: Five year utilization trends of antidotes in Iran

No.	Name (dosage form)	Price (Rials)	Volume (2004)	Volume (2005)	Volume (2006)	Volume (2007)	Volume (2008)
1	Acetylcysteine (2 g/10 mL vial)	60,300	-	-	-	-	7,370
2	Acetylcysteine (200 mg ampoule)	57,099	22,949	52,280	40,300	-	-
3	Amyl nitrite (inhalation)	14,517	360	96	4,668	55,193	15,454
4	Antibotulism polyvalent	2,300,000	1500	1490	1507	1501	1498
5	Antiscorpion venom serum	162,000	44,780	66,000	65,200	69,984	68,961
6	Antisnake venom serum	195,000	48,000	49,500	47,800	54,415	30,041
7	Atropine sulfate (0.5 mg mL <sup>-1</sup> ampoule)	800	7,956,300	6,429,690	7,680,670	6,904,120	5,156,300
8	Atropine sulfate (20 mg/2 mL ampoule)	9,000	6,110	26,710	22,310	16,470	6,920
9	Deferoxamine Mesylate (500 mg vial) *	1,550	4,714,190	5,835,160	6,344,590	5,817,180	5,497,210
10	Dimercaprol (200 mg/2 mL ampoule)	39,900	546	53	-	-	-
11	Dimercaprol (300 mg/3 mL ampoule)	39,900	2,866	-	5,268	1,597	-
12	Flumazenil (0.5 mg/5 mL ampoule)	119,648	9,480	10,780	14,000	10,335	7,715
13	Glucagon hydrochloride (1 mg/mL vial)	228,197	4,685	4,023	2,069	3,484	2,214
14	Methylene blue (100 mg/10 mL ampoule)	37,165	-	-	550	150	-
15	Naloxone hydrochloride (0.4 mg/mL ampoule)	1,666	1,091,860	1,588,200	1,686,870	1,062,076	567,520
16	Obidoxime chloride (250 mg/mL ampoule)	21,867	3,203	1,530	2,135	900	-
17	Penicillamine (250 mg capsule)	3,104	540,000	798,650	25,000	732,130	757,230
18	Pralidoxime (1000 mg vial)	16,605	25,571	36,305	54,735	-	-
19	Pralidoxime (200 mg/10 mL vial)	11,000	-	-	1,685	14,288	-
20	Protamine sulfate (100 mg/10 mL vial)	24,005	200,346	186,806	225,922	167,463	12,020
21	Protamine sulfate (50 mg/5 mL vial)	12,000	-	-	-	145,723	120,125
22	Sodium nitrite (30 mg/mL ampoule)	505,000	-	50	70	-	-
23	Sodium thiosulfate (12.5 g/50 mL vial)	105,689	42	173	186	74	-
24	Succimer (100 mg capsule)	80,400	100	100	2,150	600	-
25	Vitamin K1 (10 mg/mL ampoule)	1,389	1,142,593	806,803	850,485	747,741	367,355
26	Vitamin K1 (1 mg/0.5 mL ampoule)	865	1,165,852	1,284,210	1,260,290	1,378,030	1,218,180

shown in Table 3. For all registered antidotes, the amount of accessibility in each year are indicated during last five year from 2003 to 2008. Assessment of requirement for each of them during different years as a trend of usage has been useful for decision makers to better shape the health policy.

## DISCUSSION

Regarding obtained results in terms of availability, IDL include most of antidotes. It should be mentioned that special kind of official registration for pharmaceutical products exists in Iran. Firstly, a committee accepts adding of a drug to IDL and then to ensure its availability and then in case of demand to make them accessible, other registration process is implemented. Results show that only 60% of antidotes of IDL have been registered and are accessible in the market. The volume of utilization of existing antidotes during 5 years indicate that 25% of them are almost expensive (more than 40000 Rials or 10 dollars) that is 1% of expenditure basket of Iran. All antidotes are under umbrella of insurance while as an exception, there is a 90% extra subsidization for deferoxamine mesylate as antidote for iron because of its use in thalasemic patients and also its new indications in lung diseases (Mousavi *et al.*, 2010).

For better accessibility, almost all of these antidotes are available in the referral poisoning hospitals which are specialized for toxicology services and are covered by insurance services. In other words, eighty percent of the

prices of these antidotes are paid by the insurance companies to make them affordable.

As shown in Table 3, consumption of atropine sulfate 0.5 mg/1 mL ampoule in terms of volume is diminished during 5 years because of adding atropine sulfate 20 mg/2 mL ampoule to IDL. Data indicate that the change in dose of atropine not only reduced the total number of atropine 1 mL used but saved nursery time and the package cost. This led to a kind of cost reduction in terms of economics scale. Results also indicated that use of naloxone HCl 0.4 mg/1 mL ampoule has been reduced in the last 5 years which might be an evidence for change of usage of the opioid narcotics or related products (Shadnia *et al.*, 2007). The use of amyl nitrite ampoule has been increased more than 10 times comparing with the average use of this product during the 5 years. At the present, there seems no toxicological reason for use of this antidote. Surprisingly the increased use of amyl nitrate is associated with a reduced usage of sodium nitrate and sodium thiosulfate. The first thing that comes to mind is that amyl nitrate is being abused for unknown purposes.

The total unit of protamine sulfate consumption has been decreased during last 3 years and this is compatible with the use of heparin during these years. Three years ago, low molecular weight heparins like enoxaparin sodium and dalteparin sodium were registered and entered to the Iranian market that has resulted in lower use of protamine sulfate.

In most of the countries, one of oximes (pralidoxime or obidoxime) has been registered and is available for organophosphate poisonings (Rahimi *et al.*, 2006) but both of these antidotes are within IDL and available in the market. Regarding higher price of obidoxime and its higher rate of side effects in comparison to pralidoxime, it seems rational to exit one of them from IDL. Results also indicate that despite of adding of intravenous ethanol to IDL (Table 2), the real demand of this product is not clear and therefore none of domestic manufacturers tried to produce or import it to the Iranian market. The reason behind this defect returns to lack of information or ineffective relationship between drug department of the government and the importers or manufacturer companies and poisoning centers. As shown in Table 3 for polyvalent anti-botulism there was fixed amount of utilization during last 5 years that is the outcome of special limitation rule of national regulatory to restrict cosmetic use of this antidote.

Total medicines which were used in Iran during the year 2008 was 39.85 USD per capita in terms of value and 439 per capita in terms of volume. The total amount of antidotes that were used at the same period in terms of value was 0.05 USD per capita and in terms of volume was 0.2 per capita. Among a total of 40000 physicians who are working in Iran, clinical toxicologists are estimated 30-50 working in only 10 hospitals in the country that have special poisoning management services. Surprisingly, in spite of lack of adequate healthcare services in clinical toxicology, epidemiological data show that the most inpatient diseases in the country that result in hospitalization is poisoning and the poisoning is the second most common cause of mortality in hospitalized patients (Anonymous, 2008).

### CONCLUSION

Regarding multi-purpose usage of antidotes and lack of accurate data and information about poisoning, it is too hard to estimate the real demand for antidotes. Sometimes lack of adequate information about access to antidotes and sometimes high prices of them are barriers of good management of poisoning that result in defective strategic depot of the antidotes in the country. Effective impact of poisoning in economical and social concerns of the life necessitates implementation of stronger policies in clinical toxicology matters.

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