Journal of the Islamic University of Gaza, (Natural Sciences Series) Vol.12, No.1, PP.25-36 2004

# UTILIZATION OF ACETAMINOPHEN IN PALESTINE:TOXICITY AND THERAPEUTIC IMPLICATIONS

**Waleed M. Sweileh,** College of Pharmacy, An-Najah National University, Nablus, Palestine. E-mail: *waleedsweileh@yahoo.com*

## استعمال دواء (الأسيتامينوفين) في فلسطين: الدلالات الدوائية والسمية

**الملخص** على الرغم من أن طريقة عمل دواء الأسيتامينوفين غير معروفة، إلا أن هذا الدواء هـو أكثـر دواء استعمالا" بين الأطفال والكبار كمسكن للألم وخافض للحرارة. لا توجد دراسات في فلسطين عن مدى وطبيعة استهلاك هذا الدواء ودلالتها العلاجية والسمية. أن الهدف من هذه الدراسة هو تحليل نمط استخدام دواء الأسيتامينوفين ودلالته العلاجية والسمية ولقد قمنا بذلك عن طريق تحليل وصفات الأسيتامينوفين في سنة 2000 وتحليل مبيعات الأسيتامينوفين بغير وصفة من الصيدليات العامة عن طريـق اسـتبيان 118 صيدليه من أصل حوالي 620 صيدلية في فلسطين. تحليل البيانات أشار إلـى أن 3925 (14.7%) مـن الوصفات تحتوي على دواء الأسيتامينوفين مما يدل على أن كل سابع مريض في عيادة طبية يوصف لـه دواء أسيتامينوفين. التحليل أشار أيضا إلى أن اكثر من 50% من هذه الوصفات قـد صـرفت للأطفـال والرضع. تحليل نتائج مبيعات الأسيتامينوفين بغير وصفة أشارت إلى أن حوالي 6026400 علبـة دواء اسيتامينوفين يتم بيعها سنويا على الأقل مما يشير إلى أن الأستهلاك الفردي لهذا الدواء هو حـوالي 20.4 غم في السنة. يتم بيع كمية أسيتامينوفين من الصيدليات بغير وصفة بقيمة حوالي 10668350 مليـون دولار سنويا . نقترح وضع قوانين جديدة وعمل نشرات تثقيفية عن سمية الأسـيتامينوفين للتقليـل مـن الاستهلاك العشوائي لهذا الدواء بغرض التقليل من التأثير السمي التراكمي بين المرضى في فلسطين.

**Abstract** Although its therapeutic mechanism of action is uncertain, acetaminophen (APAP) is one of the most commonly used analgesic antipyretic drug among children and adults. No studies were conducted on the pattern and extent of utilization of analgesics and APAP in particular in Palestine. The objective of this study is to analyze patterns of prescription and nonprescription of (APAP) use among the general Palestinian population. The prescribing patterns in Palestine for (APAP) were studied by analyzing the 2002 prescription database. The non-prescription sale was obtained by a survey of 118 out of approximately 620 community pharmacies in West-Bank. Analysis showed that 3925 (14.7%) prescriptions contain an APAP products suggesting that at the national level, every seventh patient to a doctor's clinic receives an APAP or APAP containing product. More than 50% of these APAP prescriptions were dispensed for children or infants. Analysis of APAP non-prescription sale showed the annual sale of APAP in community pharmacies in West-Bank regardless of dosage form is approximately 6,026,400 box suggesting that annual consumption rate of APAP

per capita in Palestine is 20.4 gram/inhabitant/year. The national expenditure on APAP bought as an over-the-counter (OTC) from community pharmacies is estimated to be 10,668,350 million USD per year. Legislative actions and health awareness are needed to reduce consumption of APAP and risk of its toxicity among the general population.

## Introduction

Acetaminophen (paracetamol = N-acetyl-para-aminophenol [APAP]) is a non-narcotic analgesic and antipyretic drug [(1)]. It was discovered by Cahn and Hepp in 1886, and was first used in 1893 and has been an over-the-counter (OTC) drug since 1955 [(2)]. The mechanism of action of APAP is not clearly understood yet. It is a weak inhibitor of prostaglandin synthesis, has very little anti-inflammatory effect when compared to acetylsalicylic acid and also lacks the blood thinning and gastro-toxic effects typical of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) [(3-5)]. Recently, in a paper published in the October 15, 2002 issue of *Proceedings of the National Academy of Sciences*, Chandrasckharan and colleagues reported a new cyclooxygenase-1 (COX-1) variant that they have called COX-3. As with other COX enzymes, COX-3 is involved in prostaglandin synthesis. COX-3 is selectively inhibited by acetaminophen, phenacetin, antipyrine, and dipyrone [(6)]. APAP is absorbed well from gastrointestinal tract and is metabolized in the liver, where approximately 90% of the drug is metabolized into glucuronide and sulfate conjugates [(7)]. Both conjugates are excreted readily by the kidneys. A small fraction of acetaminophen (2% to 4%) is eliminated by the kidneys without being altered. A similar percentage is metabolized by a hepatic cytochrome P-450 enzyme and yields a toxic intermediary N-acetyl-para-benzoquinoneimine (NABQI). This toxic intermediary combines with hepatic glutathione to be converted to cystine and mercaptate, which are readily excreted in the urine [(8)]. Over-utilization of the cytochrome P-450 pathway by excessive acetaminophen produces excess (NABQI), which subsequently depletes hepatic glutathione. With glutathione depleted, the toxic product (NABQI) accumulates, leading to hepatic necrosis [(9)]. In Palestine, APAP is available in many prescription and nonprescription (OTC) formulations. It is available alone or in combination with numerous other drugs including anti-cholinergics, antihistamines, caffeine, barbiturates, and narcotics. In Palestine, there are at least ten brand names of APAP or APAP- containing formulations: (e.g. Febramol®, Paracare®, Acamol®, Sedamol®, Gamased®, Dexamol®, Otamol®, Pamol®,

Abrol®, Cod-Acamol®, Paracod®, Dexamol Plus®, Dexamol Day and Night®, Sedamol Day and Night®, Algolysin®, Analgan®, Algonal®, Rokacet®, Norgesic®, Muscol, ® Balgesic®, Paraflu®, Flu® and many others). Most of these brand names are available in different pharmaceutical dosage forms like tablets and caplets for adult use; syrup and suppositories for children and infant use. These brand formulations contain 500 mg APAP / tablet or 125 mg / 5ml syrup. These APAP brand formulations are available at a price range of 0.7 USD up to 2.9 USD per box regardless of dosage. The average price of APAP brand formulations is 1.75 USD which is relatively inexpensive. In Palestine, most patients seek self medication for mild to moderate pains directly from community pharmacies because they are faster and less expensive than doctor's clinics. With its safe profile on stomach, low cost and over the counter convenience, APAP has become the drug choice for many physicians, community pharmacies and patients in treating mild to moderate pain with or without fever. Unfortunately, the wide range brand availability of APAP, status as an over-the-counter (OTC) drug, lack of national poisoning data on APAP and lack of health education and awareness has perpetuated the belief that APAP is completely benign. Actually, APAP is one of the most potentially dangerous analgesic drugs. An intentional overdose can be fatal, and chronic use may cause liver and kidney damage [(10-15)]. Very few pharmco-epidemiology studies were carried out in Palestine to assess the utilization and prescribing pattern of analgesics. Furthermore, there is no public official or documented data on either intentional or non-intentional analgesic or APAP poisoning in Palestine. The aims of this study are to assess the prescribing pattern and prescribing prevalence of APAP among medical practitioners and to assess the non-prescription (over-the-counter; OTC) sale of APAP in community pharmacies in Palestine with the ultimate goal being to estimate the consumption of APAP in the Palestinian community with reference to possible toxic implications.

**Methods**

The data on prescribing prevalence of APAP was obtained by analysis of prescription database created for the year 2002. The prescription database was created by collection 26,631 prescriptions dispensed in community pharmacies in the major districts in West-Bank of Palestine. Collection included community pharmacies in cities, villages and camps and the

collection of the prescription was made by An-Najah fourth and fifth grade pharmacy students. The non-prescription utilization of APAP was made by a survey on the over-the-counter sale of APAP in the community pharmacies. The survey included 118 out of approximately 620 community pharmacies in all areas of West-Bank in Palestine. All data analysis and graphics were processed using excel soft ware.

## Results

Analysis of the prescription database showed that 3925 (14.7%) prescriptions dispensed in community pharmacies during the year 2002 contain an APAP products. The prescription database showed that 6977 prescriptions (26.2%) dispensed in community pharmacies during the year 2002 contain NSAIDs or non-APAP (opioids or other centrally acting) analgesics (Figure 1). This suggests that at the national level, every fourth patient receives an NSAID / non-APAP analgesic medication and every seventh patient to a doctor's clinic receives an APAP or APAP containing product. The majority of APAP prescriptions (>50%) contain plain APAP products while the rest contain combinational products (e.g. APAP with codeine, APAP with dextropropxyphene, APAP with pseudoephedrine and others). Further analysis of APAP containing prescriptions showed that 49.2% of these prescriptions contain APAP tablets / caplets while 42.8% contain APAP syrup and 8% contain suppositories assumingly dispensed for children or infants.

**Figure 1: Analysis of 2002 prescription database in Palestine**

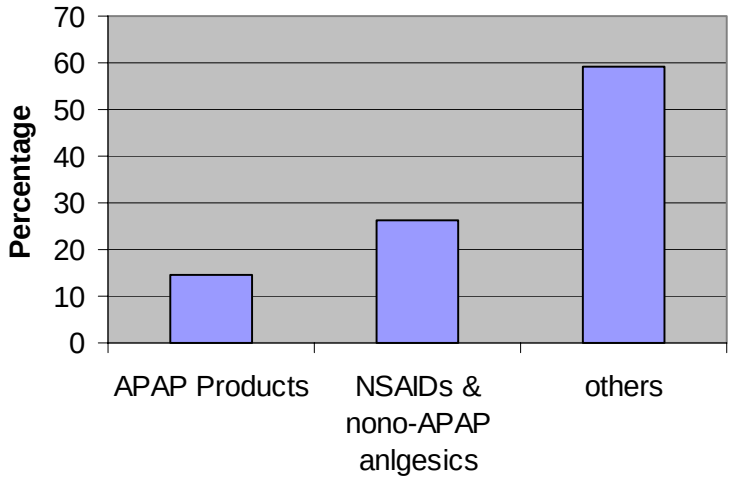
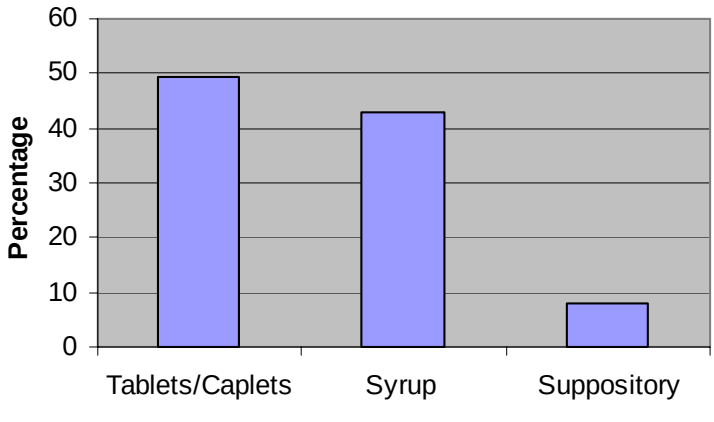



**Figure 2: Analysis of APAP prescriptions**



Cross tabulation of age versus number of APAP prescriptions showed that 3165 (69.6%) prescriptions were for patients aged one day up to 12 years of age (Table 1).

Table 1: Age and APAP prescription frequency.

| Age category (years) | Frequency of prescriptions | Percentage |
|---|---|---|
| Up to 12 years | 3165 | 80.6% |
| More than 12 years | 760 | 19.4% |
| Total | 3925 | 100% |

Cross tabulation of the APAP prescriptions with drugs concomitantly prescribed with APAP in the same prescription showed that in 68.7% of the prescriptions, APAP was co-prescribed with an antibiotic (Table 2).

Table 2: Frequency of drug classes co-prescribed with APAP in the same prescription. Frequencies are overlapping.

| Drug Class Co-Prescribed with APAP | Frequency of prescriptions containing that drug class. | Percentage of prescriptions containing that drug class. |
|---|---|---|
| Antibiotics | 2193 | 69.2% |
| Cough / Cold Preparations | 1643 | 51.9% |
| Respiratory / Asthma | 481 | 15.1% |
| Topical Preparations | 109 | 34.4% |
| Miscellaneous | 48 | 1.5% |
| None | 411 | 12.9% |

Note that the total does not need to be 100% because several drugs may be co-prescribed together in the same prescription and thus the percentages are overlapping.

Analysis of the survey data on APAP over-the-counter sale (OTC, non-prescription) showed that the sale is in the range of 4 up to 80 packs per day with an average of 27 boxes per day regardless of the APAP dosage form. Age cross-tabulation with APAP non-prescription sale shows similar results to those for APAP prescription where approximately 58% of non-prescription APAP sale was intended for children under the age of 12 years of age. Since the number of community pharmacies in the West-Bank of Palestine is approximately 620, then the annual sale of APAP in community pharmacies regardless of dosage form would be ( 27 box/day x 30 day/month x 12 month/year x 620 community pharmacy = 6,026,400 box / year). The

total amount of APAP is 10 grams / box of tablets and 2.5 grams / bottle of syrup. So the rough average of the amount of APAP would be approximately 6.25 grams per box regardless of the dosage form. Based on this, we can estimate the "minimum" annual amount of APAP consumption through community pharmacies to be: (6,026,400 APAP box / year x 2.5 gm / box = 37,665,000 gram/year = 37.6 ton/year). The actual total consumption must take into consideration the amount of APAP dispensed in hospitals, charitable clinics, prescription sale and non-pharmacy outlets. Unfortunately, such data is not available at least for the public. The number of population in Palestine is estimated to be 1.87 million [(16)]. Thus the "lowest" possible annual consumption rate of non-prescription APAP per capita in Palestine is: (37,665,000 gram/year / 1,870,000 inhabitants = 20.4 gram/inhabitant/year = 3.26 box/inhabitant/year of APAP regardless of brand name or dosage form). The average price of one box of APAP regardless of brand name or dosage form is 1.75 USD / box, then the national expenditure on APAP dispensed as an OTC from community pharmacies would be: (3.26 box/inhabitant/year x 1.75 USD/box x 1,870,000 inhabitant = 10,668,350 million USD/year). The minimum overall consumption of APAP by a Palestinian citizen during an average life span of 60 years would be: (3.26 box/inhabitant/year x 60 years = 195.6 box / life span which is equivalent to 1,222 grams or 1.22 kg of APAP. This is at least one and a half times more than the total amount of atenolol 100 mg taken once daily by a hypertensive patient for twenty years (0.1 gm / tablet/day x 30day/month x 12month/year x 20 year = 0.72 Kg in 20 years).

Estimation of the consumption of prescription and non-prescription APAP by specific age group, infant/children who are less than 12 years of age would yield different values than those calculated per capita. Since approximately 80% of the APAP non-prescription sale is for infants/children then if we multiply the total APAP non-prescription utilization by 80%, we will get the following:

37,665,000 gram/year x 80% = 30132000 gram APAP/year consumed by infant/children in Palestine. The approximate percentage of children under the age of 12 in West-Bank is approximately 40% (0.72 million) [(16)] . Thus, the average non-prescription consumption of APAP would be:

{30132000 gram /year / 720,000 children = 41.85 gram / year / child}.

The estimation of the prescription APAP consumption per child per year would be as follows assuming that each prescription contains one box of APAP regardless of the dosage form:
{3165 prescription/year x 6.25 gm APAP/box /prescription = 19781.25 gm /year}. Calculating the average prescription consumption of APAP / child /year would be:
{ 19781.25 gram/year / 720,000 children = 0.027 gram / child / year}.
Thus the total consumption of both prescription and non-prescription APAP per child per year in Palestine would be:
41.85 gram / year / child + 0.027 gram / child / year = 41.87 gram/child/year. This is the lowest possible estimate because the APAP consumption by children through governmental clinics was not taken into consideration because of lack of such data.

## Discussion

Pain is the leading symptom of most diseases and patients have always tried to overcome pain using physical and chemical means. The ready availability of over-the-counter APAP and other analgesic products means that much of the mild to moderate pain problems in the community is self-medicated. However, it is vital that the general public be aware and updated on the real hazards of these pain killers. The analysis of prescription database and non-prescription (OTC) APAP sale indicates that there is an over-use or misuse of analgesics in general and APAP in particular. Although, the annual consumption of APAP based on our estimation is still far below the reported amount of potential APAP toxicity, nevertheless, our concern is the cumulative and chronic toxicity as well as the potential possible harm of the concomitant use of APAP with antibiotics or other drugs for children. The total of 1.22 kg (see results) of APAP consumption during an individual's life span is worth investigating the possible toxic consequences. The high prescribing rate of APAP for children and infants is inappropriate (see table 1). This increased use of APAP in young children is due, in part, to concerns over the association of Reye's syndrome with aspirin. APAP is reported to have serious immunosuppressant effects that may not be a secondary response to APAP-hepatitis, but a primary response to APAP [17, 18]. Given the fact that APAP is mostly used to reduce fever associated with infection among children (see table 2), then the immunosuppressant effect of APAP would have very serious clinical consequences. Of another clinical

significance is the recent reports of APAP cross-reaction with aspirin at a rate of approximately 20 - 30% in a dose-dependent way among analgesic intolerant asthmatics [19]. Approximately 15% of the APAP prescriptions contain respiratory and anti-asthma drugs which should raise clinical concern among the medical practitioners. Therefore, APAP should not be recommended to analgesic intolerant asthmatics, without performing oral provocation tests to prove its safety. The pattern of misuse/overuse of analgesics in general and APAP in particular is also noticed in other developed countries like United Kingdom and USA where APAP is one of the most commonly used substance in deliberate self poisoning. In these two particular countries, APAP was the commonest drug used in overdose [20, 21]. In England and Wales, APAP was involved in 48.3% of the 18,000-19,000 hospital-referred cases of self poisoning during 1988 – 1989 [20]. Each year in the United Kingdom roughly 2600 million tablets of APAP are sold over the counter and 600 million supplied on prescription (Paracetamol Information Centre, 1993 study) [22]. The total analgesic consumption per capita in Germany was highest in Europe and estimated to be 18.2 gram /capita / year which is far less than our estimate per Palestinian inhabitant per year [23]. The use of APAP in deliberate self-poisoning in Germany was12.4 % of the total self-poisoning cases in 2002 [24]. In the USA, APAP sale accounted for approximately 300 million USD of the 1.2 billion USD spent on analgesic medication during the early 1980s [25].

In Palestine, preventive measure must be taken to limit this overuse/misuse of APAP. A new national policy like new legislations or health awareness campaign among the public and health professionals is needed. The new suggested legislations might be directed toward restricting the sale of APAP to community pharmacies and prohibiting the sale of APAP in non-pharmacy outlets. The legislation might also consider changing the status of APAP from OTC to *Prescription only* or changing the pack size to reduce the total consumption. In other countries, such suggested legislation has been shown to reduce the risk of analgesic self harm or non-intentional poisoning [26, 27]. Patients should be encouraged to use an alternative OTC analgesic like 200 mg ibuprofen which has a safer hepatic toxicity profile than APAP. Ibuprufen and other NSAIDs have greater adverse effects in therapeutic use than APAP but also have a lower incidence of severe features or death in acute or chronic overdose. Unfortunately, aspirin carries both significant

adverse effects in therapeutic dose and a substantial risk in overdose, for which there is no antidote. Another method to reduce overall APAP over-use would be to include clear warning on APAP in patient package inset regarding possible hepatic toxicity. A review of the language used in the patient package insert of most brand names of APAP showed that the manufacturers fail to give a specific warning or precaution regarding possible hepatic damage upon overdose or chronic use. Unfortunately, this failure to give a clear precaution language in patient package insert created the misconception among the public that APAP is a safe drug. The ministry of health (MOH) in Palestine should demand the local manufacturers to use a clear precaution language in APAP package inserts. Finally, we can not correlate the results obtained from this study with APAP-induced mortality or morbidity data in Palestine since such data are not available. Furthermore, based on our results, we can not strongly claim that there is such correlation. However, the ideas brought up in this project worth further evaluation and study.

**References**

1. Linden, CH. Acetaminophen. In: Tininalli, ed. *Emergency Medicine: A Comprehensive Study Guide*. 4th ed. New York, McGraw Hill. **1996**: 787-792.

2. Mering, von, J. Beiträge zur Kenntniss der Antipyretica, *Therap. Monatshefte*, **1893**,7, 577-578.

3. Skjelbred P., Album B., Lokken P.: Acetylsalicylic acid versus paracetamol effects on post-opertaive course. *Eur. J. Clin. Pharmacol*. **1977**; 12: 257-64.

4. O'Brien JR. Effect of anti-inflammatory agents on platelets. *Lancet*, **1968**; 1: 894-5.

5. Jick H. Effects of aspirin and paracetamol on gastrointestinal hemorrhage: results from the Boston Collaborative Drug Surveillance Program. *Arch Int Med.* **1981**; 141: 316- 21.

6. Chandrasckharan NV., Dai H., Turepu Roos KL., et al. COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: Cloning, structure, and expression. *Proc Natl Acad Sci USA* **2002**;99(21):13926-31.

7. Studenberg SD., Brouwer KL. Hepatic disposition of acetaminophen and metabolites. Pharmacokinetic modeling, protein binding and subcellular

distribution. *Biochem Pharmacol* **1993** Aug 17;46(4):739-46.
8. Watari N., Iwai M., Kaneniwa N. *Pharmacokinetic study of the fate of acetaminophen and its conjugates in rats. J Pharmacokinet Biopharm,* **1983** Jun;11(3):245-72
9. Matthews AM., Roberts DW., Hinson JA., Pumford NR. Acetaminophen-induced hepatotoxicity. Analysis of total covalent binding vs. specific binding to cysteine. *Drug Metab Dispos* **1996** Nov;24(11):1192-6
10. Lane JE., Belson MG., Brown DK., Scheetz A. Chronic acetaminophen toxicity: a case report and review of the literature. *J Emerg Med*. **2002** Oct;23(3):253-6.
11. McLaughlin JK., Blot WJ., Mehl ES., Fraumeni JF Jr. Relation of analgesic use to renal cancer: population-based findings. *Natl Cancer Inst Monogr*. **1985** Dec;69:217-22.
12. Blakely P, McDonald BR. Acute renal failure due to acetaminophen ingestion: a case report and review of the literature. *J Am Soc Nephrol*. **1995** Jul;6(1):48-53. Review.
13. Keaton MR. Acute renal failure in an alcoholic during therapeutic acetaminophen ingestion. *South Med J*. **1988** Sep;81(9):1163-6.
14. Kaysen GA., Pond SM, Roper MH., Menke DJ., Marrama MA. Combined hepatic and renal injury in alcoholics during therapeutic use of acetaminophen. *Arch Intern Med*. **1985**; Nov;145(11):2019-23.
15. Bonkovsky HL., Kane RE., Jones DP., Galinsky RE., Banner B. Acute hepatic and renal toxicity from low doses of acetaminophen in the absence of alcohol abuse or malnutrition: evidence for increased susceptibility to drug toxicity due to cardiopulmonary and renal insufficiency. *Hepatology*. **1994** May;19(5):1141-8.
16. Palestinian Central Bureau of Statistics (PCBS): *Main findings, Population survey*, Ramallah, Palestine, **1998**.
17. Ueno K., Yamaura K., Nakamura T., Satoh T., Yano S.*:* Acetaminophen-induced immunosuppression associated with hepatotoxicity in mice. *Res Commun Mol Pathol Pharmacol*. **2000**;108(3-4):237-51
18. Yamaura K., Ogawa K., Yonekawa T., Nakamura T., Yano S., Ueno K. Inhibition of the antibody production by acetaminophen independent of liver injury in mice. *Biol Pharm Bull* **2002** Feb;25(2):201-5
19. Karakaya G., Kalyoncu AF. Paracetamol and asthma**.** *Expert Opin Pharmacother* **2003** Jan;4(1):13-21

20. Hawton K, Fagg J. Trends in deliberate self poisoning and self injury in Oxford, 1976-90. *British Medical Journal*. **1992**;304:1409-11.
21. Litovitz TL., Felberg L., Soloway RA., Ford M., Geller R.1995 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med* **1995**;13:551-97.
22. www.pharmweb.net/pwmirror/pwy/paracetamol/pharmwebpic.html
23. Pommer W., Glaeske G., Molzahn M. The analgesic problem in the Federal Republic of Germany: analgesic consumption, frequency of analgesic nephropathy and regional differences. *Clin Nephrol* **1986** Dec;26(6):273-8
24. Von Mach MA., Lauterbach M., Kaes J., Hengstler JG., Weilemann LS. Deliberate self-poisoning with paracetamol (acetaminophen): an analysis from 1995 to 2002. *Dtsch Med Wochenschr* **2003** Jan 3;128(1-2):15-9.
25. Consumer Expenditure Study, Internal Analgesics. *Product Marketing and Cosmetic and Fragrance Retailing*. 10:38, **1981**.
26. Prince MI., Thomas SH., James OF., Hudson M. Reduction in incidence of severe paracetamol poisoning. *Lancet.* **2000** Jun 10;355(9220):2009-10.
27. Hawton K: United Kingdom legislation on pack sizes of analgesics: background, rationale, and effects on suicide and deliberate self-harm. *Suicide Life Threat Behav* **2002** Fall;32(3):223-9