

# Patient's Safety Information Available On Drug Package Inserts Used In Neuroanesthesia

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## Abstract

Background: Information on drug inserts is an important for patients and physicians regarding the safety and proper administration of a drug. Recent studies have found that key information regarding drug's safety are still missing. The aim of this study was to ascertain whether or not inserts, in King Fahad Medical City (KFMC) Riyadh, of neuroanesthesia drugs were deficient with respect to safety and efficacy. Method: Study evaluated the inserts of 48 medications used in routine neuroanesthesia practice in the department against a set of three safety criteria Drug interactions information, Hypersensitivity and general precautions. Results: Inserts were variable in several safety categories for neurosurgical patients, Drug interaction was mentioned in 76%, Hypersensitivity in 76% and general precaution in variable health conditions were in 82% if the drug inserts. The quality of information was poor in drugs coming from developing countries versus those drugs coming from North America and Europe. 90% of inserts were directed to medical staff, which is going to use it. Only 10% had information directed to patient directly or indirectly through physician warning Conclusion: The pharmaceutical industry should address this as well as implement the patient safety of dangerous drugs, depending on available animal or human studies.

## INTRODUCTION

In 2006, U.S.A.'s Food and Drug Administration (FDA) unveiled a major revision to the format of prescription drug information, appearing on the package insert, to give healthcare professionals clear and concise prescribing information. It is intended to have the most up-to-date information in an easy-to-read form that draws physician and patient attention to the most important drug information before a product is prescribed.

Pharmaceutical preparations package insert is an essential feature of drug packaging. It is present in most of the medicines; [1]. It is considered as the primary source of information for health care providers about drugs [2]. Package's insert is also, a legally required document intended to inform the user of the approved and off label uses of the drug, its dose and any contraindications or adverse effects [1]. Mostly, it is an effective mean to communicate about the risks of drugs [3], and it has an important impact on patients compliance and thus on the ultimate effectiveness of drug use [4]. To achieve its goals, the drug's insert should be clear and comprehensible to convey the intended use of the product, provide an adequate directions for use, warn against potential harmful effects and

provide instructions for appropriate length of treatment and when to seek medical advice [5]. Neuroanesthesia used drugs may interact with other anesthetic drugs and any other drugs the patient is taken in the perioperative period. The neuroanesthesia drugs are usually used by medical and nursing staff of the hospital and not the patient self administered. So it has to be seen if their insert have enough information to alert the practitioner about such precautions of use.

Some studies appeared in recent months' investigation studying the general qualities of drug insert qualities regarding safety precautions and it demonstrated to be inadequate. Recently a publication from our department prepared to examine the anesthesia drug insert's qualities of information in our hospital [6]. In this paper a report on the quality of patient safety information contained in drugs inserts used in Neuroanesthesia.

Drug interactions (DI), represent one of the most common forms of adverse drug related events but widely under-recognized source of medical errors [7,8,9,10]. Although, some drug interactions can also be beneficial, they can be harmful either by increasing the toxicity of a drug or by reducing its

efficacy [1011]. Thus, the consequences of being exposed to an interaction are not trivial. and it has enormous impact on total patient care including the risk of increased hospitalization [1213]. Preventable drug interactions account for about one third of adverse drug effects but incur about one half of the total adverse effect costs [710]. It is imperative to say that anesthesia practice depends in part on the proper use of such beneficial DI like sedation and analgesia or hypnotic effect of groups of drugs. Still the dangerous DI should be prevented otherwise it may set-in.

Several studies found between 2.2% and 70.3% patients may be affected by potential DI [11]. Other studies have reported that the incidence of DI ranges from 3% to 30% [8]. Again, a number of studies have also estimated the incidence of potential DI in 20-30% of patients with clinically relevant interactions at 4-10% [8,14,15]. Although, not all drug interactions are clinically significant, it is important to be alert for those that are. But, it is impossible to remember all the known important drug interactions; however, knowledge of the main types of DI will act as a useful alert when prescribing [11]. To treat patients in a competent and safe manner, some awareness of the DI issue and some means of detecting DI are essential [13].

In a recent study on DI [15] in a developing country it was found that no adequate information on DI is available in spite that drug package inserts are likely to be of great importance in the developing countries, where electronic drug alert systems, especially computer-assisted detection of drug interactions are virtually absent. From healthcare professionals to the patients, drug inserts provide most of the information relating to adverse drug reactions, which can be lifesaving [17]. This study conducted an analytical study to explore the extent and nature of information presented in neuroanesthesia drug package inserts of most commonly drugs used at King Fahad Medical City (KFMC) in Riyadh KSA. We particularly emphasized on DI, hypersensitivity and neurological precautions of use.

## **METHODS**

### **SAMPLE SELECTION**

The basic list of drugs supply used routinely during neuroanesthesia was selected for the study. The drug package's insert was read and analyzed to verify the three items related to patient safety namely the DI, Hypersensitivity and precautions of use. Package inserts of the selected products were obtained from the drug packages available with the presented drugs or from general store of

Hospital pharmacy for hospital packs, we could not perform randomization of samples. For this we gathered a small convenience sampling of 48 package-inserts from different drug manufacturers during October 15 th , 2007 to March 15 th 2008. Repeated inserts for the same drugs were excluded from the study.

## **DATA ANALYSIS**

The collected package inserts of different brands were sorted out according to individual drug scientific name and class. Then information were examined and analyzed to obtain necessary information by the Authors [Graduates certified anesthesiologists]. Drug inserts information was enlisted in the pre-formulated table of a personal computer. The information was further cross-checked with the help of the available published and retrievable literatures to determine any substantial omission and consistency of information in the collected package inserts. Descriptive statistical analysis was performed using Microsoft ® Excel 2007 version Windows XP Professional.

## **RESULTS**

Of the total (n = 48) package inserts, 37 (77%) contained some information on DI while 11 (23%) did not include any. Also 37 (77%) contained information on contraindications in case of known hypersensitivity and 29 (60%) contained list of precautions concerning concurrent diseases or conditions. Number of package inserts containing precautions information was greater for narcotics, intravenous anesthetic agents, inhalational anesthetic agents and local anesthesia agents' injections. A summary of drug package inserts containing information on DI, hypersensitivity and specific precautions appear in (Table 1).

**Figure 1**

Table 1: Breakdown number of package inserts information [N 50 (100%)]

	With information	No information
Type of information	N (%)	N (%)
Drug interactions (DI)	36 (75)	12 (25)
Hypersensitivity	36 (75)	12 (25)
Precautions	29 (60)	19 (40)

Textbook's information on DI was not mentioned except in 4 drugs (8%). But none mentioned any rate of occurrence or morbidity of these incidences. Also, there were no statements specifying the DI as dangerous or potential or clinically significant in those package inserts. In most of the cases, no mechanisms were stated to avoid or to reduce the

incidences of common DI. A short description of the

information on DI extracted from the drug package inserts have been provided in the table 2.

Figure 2

Table 2: Types of precautions for drug actions presented in the package inserts. Characteristics of Precautions concerning CNS in (29 ubsert 60%) Anesthetic Drugs Package Inserts

Name of drugs	Effects on CNS
Glycopyrrolate	lower effect on CNS because blood -brain barrier passage is limited
Atropine	Tremor, fatigue, drowsiness, ataxia, mental confusion or excitement, dizziness
Etomidate	20-30% transient decrease in CBF, reduction in cerebral oxygen utilization proportional to reduction in CBF, in patients with and without intracranial space occupying lesions, etomidate induction is followed by moderate lowering of ICP, lasting several minutes.
Propofol	Administration of propofol in epileptic patients may also increase rest of seizures, not recommended for ECT, special care should be taken in patients with increase ICP and low arterial pressure, because of risk of significant decrease of intra cerebral perfusion pressure.
Ketamine	Precautions increases cerebrospinal fluid pressure has been reported following ketamin administration, use with extreme cautions in patients with pre-anesthetic elevated CSF pressure, side effect: enhance skeletal muscle tone may be manifested by tonic and clonic movements.
Sodium Thiopental	Dosage for cerebral hypotension, convulsive state treatment
Bupivacaine (spinal)	Neurological damages rare it causes localized area of paraesthesia or anesthesia, motor weakness, loss of sphincter control and paraplegia
Lignocaine	Ovendosage effect on CNS (convulsions, unconsciousness, coma, respiratory depression up to and including respiratory arrest and shock.
Isoflurane	precautions in patients with increased ICP
Sevoflurane	In patients with normal ICP , it has minimal effect on ICP and preserved CO2 responsiveness, the safety of sevoflurane has not been investigated in patients with raised ICP. In patients with risk for increased ICP it should be administered cautiously in conjunction with ICP- reducing maneuvers such as hyperventilation. Convulsion may occur extremely rarely following sevoflurane administration particularly in children.
Morphine	contraindicated in head injury and increased ICP
Meperidine	should be avoided in patients with increased ICP or in those with convulsive states such as status epilepticus
Fentanyl	use of rapid bolus injections should be avoided in patients with compromised intra-cerebral compliance because transient decrease in MAP has occasionally been accompanied by a short lasting reduction of the CPP. Central and peripheral nervous system disorder reported in association with intravenous Fentanyl use
Hydralazine	headache (very common) dizziness (uncommon), tremor (very rare)
Nitroglycerine	Headache due to cerebral vasodilatation and is dose dependent and usually regress after a few days under continued therapy.
Metochlopramide	extra Pyramidal symptoms, use of metochlopramide may mask the clinical picture of undelined disorders such as cerebral irritation
Propranolol	Confusion, dizziness, nightmares, mood changes.
Metoprolol	Confusion, dizziness, nightmares, mood changes.
Esmolol	dizziness 3 % of patients, somnolence 3%, confusion, headache, and agitation in 2% of patiens, seizure reported in <1 % of patients with one death
Verapamil	Dizziness, headache and occasional seizures
Digoxin	Headache visual disturbances and psychosis.
Amiodarone	Ataxia very common > 10%, common > 1% to <10% headache, dizziness.
Midazolam	It has a very rapid sedative and sleep- including action of pronounced intensity. It also exerts anolytic, anticonvulsant and muscle relaxant effect, overdosage lead to coma, areflexia
Flumazenil	Seizure has been reported in pts known to suffer from epilepsy or severe hepatic impairment.
Methylprednisone	increase ICP, Pseudomotor cerebri, convulsions, psychic derangements ranging from euphoria, insomnia, mood swings
Hydrocortisone	increase ICP, Pseudomotor cerebri, convulsions, psychic derangements ranging from euphoria, insomnia, mood swings
Dexamithasone	for treatment of cerebral edema 10 ml IV followed by 4 mg every 6 hours
Phenytoin	Neurosurgery prophylactic dosage 100 to 200 mg.

The qualities of the information were evaluated into three classes Excellent, Adequate and Poor. These evaluations do not represent the quality of the drug but the comparative

thoroughness of information some drugs insert contained. All excellent information were included in drug inserts coming from USA and Europe. Table 3.

**Figure 3**

Table 3: Qualities of information and the country of origin of the drugs presented in the package inserts.

Classification	Frequency n (%)	Country of origin of the drugs
Excellent	28 (58.3)	USA, UK, France, Belgium, Italy, Switzerland, Finland, Austria, Germany
Adequate	14 (29.2)	KSA, UAE, UK, Jordan Egypt
Poor	06(12.5)	Jordan, Egypt, UK, Italy Belgium

All information were targeting medical and nursing staff in 90% of insert some 10% has included instruction to the patient either directly or as warning given by the prescribing physician to be informed to the patient.

**DISCUSSION**

This study demonstrates that the drug package inserts analyzed did include valuable information on DI, hypersensitivity and general precautions in 76% and 82% respectively. The statement- “No significant drug-drug interactions have been observed” was reported, so we considered this as positive sign that DI was considered.

In most countries, drug package inserts should provide all the necessary information in correct and easily understandable form for safe and effective use. The information should be unbiased, should not hide anything [1]. Culminating evidence from developing countries shows that package inserts often contains minimized adverse drug reactions [18]. Drug package inserts also contained either curtailed or no information on important DI or safety precaution. which is an important aspect of overall drug safety [19]. The present study found incomprehensive records of potential DI in the inserts of the most common drug.

**CONCLUSION**

It seems that the drugs available as imported drugs have variable information in drug inserts. Some do not address fully the patient safety requirements. Improvement should follow the international tendencies to improve the information on drug inserts to improve safety of the patients.

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