

Drug utilisation and off-label use of medications in anaesthesia in surgical wards of a teaching hospital

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ABSTRACT

Background and Aims: When a drug is used in a way that is different from that described in regulatory body approved drug label, it is said to be 'off label use'. Perioperative phase is sensitive from the point of view of patient safety and off-label drug use in this setup can prove to be hazardous to patient. Hence, it was planned to assess the pattern of drug utilisation and off-label use of perioperative medication during anaesthesia. **Methods:** Preoperatively, demographic details and adverse events check list were filled from a total of 400 patients from general surgery, paediatric surgery and orthopaedics departments scheduled to undergo surgery. The perioperative assessment form was assessed to record all prescriptions followed by refilling of adverse events checklist in case record form. World Health Organization (WHO) prescribing indicators were used for analysis of drug utilisation data. National Formulary of India 2011 was used as reference material to decide off-label drug use in majority instances along with package insert. **Results:** A total of 3705 drugs were prescribed to the 400 participants and average number of drugs per patient was 9.26 ± 3.33 . Prescriptions by generic name were 68.07% whereas 85.3% drugs were prescribed from hospital schedule. Off-label drugs overall formed 20.19% of the drugs prescribed. At least one off-label drug was prescribed to 82.5% of patients. Inappropriate dose was the most common form of off-label use. There was 1.6 times greater risk of occurrence of adverse events associated with the use of off-label drugs. **Conclusion:** Prescription indicators were WHO compliant. Off-label drug use was practiced in anaesthesia department with questionable clinical justification in some instances.

Key words: Adverse events, anaesthesia, drug utilisation, off-label, National Formulary of India

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INTRODUCTION

When a drug is used in a way that is different from that described in regulatory body approved drug label, it is said to be 'off-label use'. This term implies that the drug is given either for a different indication, different dose, different dosage form, different route or different age group as compared to approval criteria.^[1] In medicine, in general, several common and routine uses of drugs are actually off-label. Off-label use is not necessarily inappropriate; it may be backed by good clinical data, but that may not have been used by physicians to update the regulatory authorities.

An anaesthesiologist or perioperative physician needs to administer a variety of drugs such as sedatives, analgesics, anaesthetics and adjuvant drugs through different routes for patient comfort and safety. In this process, drugs

may sometimes be used in doses, routes or indications different than described, depending on clinician's experience and choice. For individual clinician, the absence of formal approval by drug authority is not a major impediment to use drug in actual clinical practice.

Anaesthesia techniques are varied, such as general, topical, infiltration and intravenous regional

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anaesthesia.^[2] It has been estimated that globally, 234.1 million major surgical procedures requiring some form of anaesthesia (inclusive of general or local or spinal anaesthesia) are undertaken every year.^[3]

Research has shown that medication errors in the perioperative setup are associated with 7.2% risk of patient harm as compared to medication errors in outpatient or any other clinical setup (associated with 1.8% risk of patient harm). This observed difference could be due to certain variations in the use of perioperative medication by anaesthesiologists which sometimes crosses safety network of this setup.^[4]

Lack of rigid regulatory guidelines regarding off-label drug use has left its use at discretion of the prescriber. The main concern of such use is lack of adequate safety and efficacy data in relation to the products. Moreover, during perioperative period, plenty of drugs are used and so chances of off-label use increases.^[2]

Due to difficulty in accessing patients in the perioperative period, very few studies have been done to evaluate drug utilisation and off-label use of perioperative medications during anaesthesia. Keeping these factors in mind, it was planned to conduct a study to determine the prescription pattern and incidence of off-label use of perioperative medications during anaesthesia in patients undergoing surgery and to identify the occurrence of adverse events in patients prescribed off-label drugs.

METHODS

The study was conducted after obtaining permission from the Institutional Ethics Committee. It was an observational, prospective, cross-sectional study conducted in general surgery, paediatric surgery and orthopaedics operation theatre waiting rooms and post-operative wards from July 2012 to October 2013. A total of 400 eligible patients were selected randomly without following any pattern. These included 250 from general surgery, 100 from orthopaedic and 50 from paediatric surgery departments.

Patients scheduled for surgery were included in the study. After obtaining written informed consent, demographic details were noted. All possible adverse events related to perioperative medications were enquired about in accordance with the checklist in the case record form.

Further, patients were traced respectively in their post-operative wards. Adverse events were noted both pre-operatively and post-operatively to ensure that the post-operative event is not a continuation of the event before surgery. All information was recorded from the anaesthesiologists' perioperative assessment form. This consisted of weight of patient, diagnosis, surgery performed, type of anaesthesia, associated disease and treatment and pre-operative, intraoperative and post-operative prescriptions. The intravenous fluids as prescriptions were not included in the study.

To decide whether a particular drug is prescribed off-label, National Formulary of India 2011 (NFI) was used as the sole reference material.^[5] If the drug information was not available in NFI 2011, then information was extracted from package insert of the drug. In rare cases where package inserts could not be procured, Continued Index of Medical Specialties (CIMS) was used as a reference material.

Data were analysed using descriptive statistics for drug utilisation and off-label use. Chi-square test was employed to assess the association between the off-label drug use and occurrence of adverse events. $P < 0.05$ was considered to be significant. The statistical software used was GraphPad InStat DATASET1.ISD (Windows 7, GraphPad Software, San Diego, California USA, www.graphpad.com).

RESULTS

The study spanned around 16 months and enrolled 400 patients. The age of the participants was 36.12 ± 19.24 years (mean \pm standard deviation); 315 participants were males and 85 were females.

Each patient had received maximum of three prescriptions, that is, pre-operative, intraoperative and post-operative, accounting to a total of 1200 prescriptions. A total of 3705 drugs were prescribed to 400 participants of the study. Out of these, 2381 (64.27%) drugs were prescribed pre-operatively, 654 (17.65%) intra-operatively and 670 (18.08%) post-operatively. Out of 400 patients, 209 patients were administered general anaesthesia, 156 spinal anaesthesia, 23 combined (general + epidural) anaesthesia, while 12 patients were administered local anaesthesia.

The drugs prescribed have been classified into three broad categories and are represented in Table 1 and

the analysis of the various prescribing indicators is shown in Table 2.

The drugs most commonly prescribed by brand name were buprenorphine, hydrocortisone and midazolam. About 3.81% of drugs were prescribed as short form of the drug. The drugs most commonly prescribed from outside the hospital schedule were fentanyl, ramosetron, buprenorphine and glycopyrrolate.

Fifty-four different drugs were prescribed in the entire study. Midazolam formed the highest, i.e, 7.53% of the overall drugs prescribed in the study followed by propofol 7.31%.

A total of 298 adverse events were noted in the study participants. 44.75% patients reported at least one adverse event. Out of 298 adverse events, 167 adverse events were related to general anaesthesia, 113 to spinal anaesthesia followed by 15 to combined anaesthesia and three to other anaesthesia procedures. The most common adverse events noted were nausea and vomiting in 75 patients, dry mouth in 59 patients and sedation in 38 patients. Headache was noted in 28 patients in spinal anaesthesia group.

To decide the off-label status of a drug, out of the 54 different drugs analysed, NFI 2011 was used as reference material for 40 drugs, package insert for 11 drugs and CIMS for three drugs.

Analysis of prescriptions for off-label drug use [Table 3] revealed that 20.19% of the overall drugs prescribed were off-label. 46.26% off-label drug use was due to inappropriate dose followed by inappropriate indication in 33.29% occasions. Average number of off-label drugs per prescription was 0.62, while average number of off-label drugs per patient was 1.87. Out of total 748 off label drugs, 625 off label drugs were prescribed pre-operatively and average number of off-label drugs per preoperative prescription is 1.56; moreover, 82.5% of patients were prescribed at least one off-label drug. Out of the 346 drugs which were off-label by dose, 63.3% were due to under dosage, while 36.7% were due to over dosage. Out of the 449 off label drugs, 199 were from general surgery department, 150 from pediatric surgery department and 100 from orthopaedics department. Number of off label drugs per patient was 3 in pediatric surgery department. Percentage distribution of off-label drugs is represented in [Figure 1].

The most common drug to be prescribed off-label by indication was ramosetron (not approved for post-operative

Table 1: Classification of drugs into three broad categories

Category	Drugs
Anaesthetics (n=842)	Lignocaine, lignocaine + adrenaline, bupivacaine, propofol, thiopentone sodium, ketamine, nitrous oxide, isoflurane, sevoflurane
Adjuvants (n=1208)	Atracurium, rocuronium, pancuronium, vecuronium, succinylcholine, fentanyl, buprenorphine, pentazocine, paracetamol, midazolam, diclofenac, clonidine, tramadol, dexmedetomidine
Supportive drugs (n=2050)	Ondansetron, ramosetron, metoclopramide, hydrocortisone, dexamethasone, tranexamic acid, cefuroxime, cefotaxime, ceftazidime, cefoperazone + sulbactam, piperacillin + tazobactam, amikacin, ceftriaxone, meropenem, amoxicillin + clavulanic acid, teicoplanin, metronidazole, atropine, glycopyrrolate, neostigmine, pantoprazole, ranitidine, dopamine, mannitol, O ₂ , theophylline, sodium bicarbonate, salbutamol, methylprednisolone, vancomycin, ephedrine

Table 2: Analysis of WHO prescribing indicators

Drug use indicator	Result (mean±SD) or percentage
Average number of drugs per patient (n=400)	9.26±3.33
Average number of drugs per prescription (n=1200)	3.08±2.73
Percentage of drugs prescribed by generic name (n=3705)	68.07
Percentage of drugs prescribed brand name (n=3705)	27.93
Percentage of drugs prescribed by short form (n=3705)	4.03
Percentage of drugs prescribed by injectable route (n=3705)	85.26
Percentage of drugs prescribed by inhalational route (n=3705)	14.74
Percentage of antibiotics per patient (n=400)	8.74
Percentage of antibiotics prescribed (n=3705)	8.77
Percentage of drugs not prescribed from the hospital schedule (n=3705)	15.70

SD – Standard deviation; WHO – World Health Organisation

Table 3: Distribution of off-label drug use in different categories

Category of off-label use	Indication	Dose	Dosage form	Route	Age group	Total
Number of drugs prescribed off-label	249	346	00	66	87	748
Percentage off-label of the total drugs in study (n=3705)	6.72	9.34	00	1.79	2.35	20.19
Percentage contribution towards overall off-label use (n=748)	33.29	46.26	00	8.82	11.63	100

nausea vomiting in India), while buprenorphine was the most common drug to be prescribed off-label by dose with 100% off-label usage for both drugs. Moreover, most common drugs to be prescribed off-label by route were buprenorphine and fentanyl (not approved for epidural route), and propofol by age group (not approved for

children <3 years). None of the drugs was found to be off-label by dosage considerations.

As shown in Table 4, all (100%) prescriptions for the drugs ramosetron, amikacin, dexamethasone, clonidine, buprenorphine tramadol, pantoprazole, piperacillin plus tazobactam, meropenem, cefoperazone plus sulbactam and ceftazidime were off-label. The percentage contribution of ramosetron towards off-label drug use was highest, that is, 16.76% followed by 11.99% for propofol. The total number of off-label use of drugs in Table 3 exceeds the off-label drug prescriptions in Table 4 because a prescription may be off-label for more than one category.

As shown in Table 5, Chi-square test showed that there was 1.6 times greater risk of occurrence of adverse events associated with the use of off-label

drugs. ($P < 0.05$). 47.88% of off-label drug users reported adverse event as against 30% of non-off-label

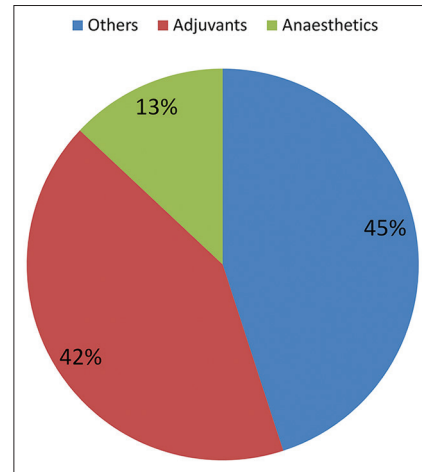


Figure 1: Percentage distribution of off-label drugs among three major drug classes

Table 4: List of off-label drugs used, their total prescriptions and percentage of off-label

Drug	Number of prescriptions	Number of off label prescriptions	Percentage of off label prescriptions	*	Category of off label drug use
Ramosetron	116	116	100	16.76	Indication
Propofol	271	83	30.63	11.99	Dose, age
Buprenorphine	61	61	100	8.81	Dose, route
Fentanyl	238	53	22.27	7.66	Dose, route, age
Glycopyrrolate	150	42	28	6.07	Dose
Dexamethasone	33	33	100	4.77	Indication
Tranexamic acid	31	31	100	4.48	Indication, dose
Vecuronium	160	29	18.13	4.19	Dose
Ondansetron	178	27	15.17	3.90	Dose
Midazolam	279	27	9.68	3.90	Dose, age
Ceftriaxone	173	21	12.14	3.03	Age
Clonidine	18	18	100	2.60	Dose, indication, route
Tramadol	18	18	100	2.60	Dose
Hydrocortisone	29	18	62.06	2.60	Indication
Amikacin	16	16	100	2.31	Indication
Atracurium	44	15	34.09	2.17	Dose, age
Pancuronium	51	14	27.45	2.02	Dose
Pantoprazole	12	12	100	1.73	Indication
Succinylcholine	14	12	85.71	1.73	Dose
Bupivacaine	196	9	4.59	1.30	Age
Rocuronium	28	8	28.57	1.16	Dose, age
Cefuroxime	82	5	6.09	0.72	Dose
Paracetamol	240	5	2.08	0.72	Dose
Ranitidine	167	3	1.80	0.43	Dose
Neostigmine	180	3	1.67	0.43	Dose
Theophylline	2	2	100	0.29	Dose
Ceftazidime	2	2	100	0.29	Indication
Meropenem	2	2	100	0.29	Indication
Cefoperazone + sulbactam	2	2	100	0.29	Indication
Dexmedetomidine	13	2	15.38	0.29	Dose
Piperacillin + tazobactam	1	1	100	0.15	Indication
Dopamine	3	1	33.33	0.14	Age
Pentazocine	9	1	11.11	0.14	Dose

*Contribution of concerned drug to overall off-label use in terms of percentage. The fixed dose combinations prescribed as off-label were piperacillin + tazobactam once and cefoperazone + sulbactam twice

Table 5: Association of off-label drug use and occurrence of adverse events

Patients	Patients with adverse events (percentage patients with adverse events)	Patients with no adverse events	Total
Off-label users	158 (47.88*)	172	330
Non-off-label users	21 (30)	49	70
Total	179 (44.75)	221	400

* $P < 0.05$ and relative risk of 1.60 (95% CI 1.097–2.323) using Chi-square test. CI – Confidence interval

drug users. There was an increasing trend in the occurrence of adverse events with increasing instances of off-label drugs encountered per patient e.g., 33.7% of patients prescribed one off-label drug each had adverse events whereas 66.6% of patients prescribed four off-label drugs had adverse events.

DISCUSSION

Our study revealed that nearly 100% of the prescriptions were complete in terms of describing the dose, route of administration, frequency and duration of treatment. This implies that basic principles of rational use of medicines were being followed at our institute.

The prescriptions by brand names in 27.93% instances can be explained by lack of training in rational use at both postgraduate and undergraduate levels along with non-availability of the drugs in generic form.^[6] Use of abbreviations to represent drug names (such as ATRA instead of atracurium) can lead to fatal consequences, if misinterpreted.^[7]

One of the positive findings was that only 15.7% of drugs were prescribed from outside the hospital schedule, largely related to the stringent regulations governing procurement and use of opioids.

In patients undergoing general anaesthesia, the most common drug used was propofol, similar to the findings by Di Filippo *et al.*^[8] Bupivacaine was the preferred drug used for induction of spinal anaesthesia in all the cases, in contrast to the study by Schiere *et al.*, wherein lignocaine was preferred in 50% cases.^[9] Variability in drug use, apprehension of transient neurological symptoms with lignocaine and availability of safer drugs such as bupivacaine in the hospital schedule can be attributed to this.

The maximum use of vecuronium could be due to its favourable pharmacokinetic profile to overcome the persistent blockade and difficulty in complete

reversal after surgery associated with rocuronium and pancuronium, similar to the findings of Zhang *et al.*^[10]

Amongst antibiotics, the higher use of ceftriaxone was in agreement with a plethora of guidelines and studies reporting and recommending the use of third generation cephalosporins for surgical prophylaxis.^[11]

We found that overall, 20.19% of drugs prescribed in the study were off-label with 82.5% of patients prescribed at least one off-label drug. A retrospective study by Doherty *et al.* in 2009 from a Canadian Paediatric Intensive Care Unit and Neonatal Intensive Care Unit reported that 59.4% of drugs were off-label and 89–99% of the patients were administered at least one off-label drug.^[12] This study included paediatric population as against our study wherein paediatric population consisted of 12.5% of the total, so the overall off-label drug use was less in our study.

Interestingly, the most common form of off-label use in our study was in the form of inappropriate dose followed by inappropriate indication. This finding was quite similar to that by Doherty *et al.*, and Bavdekar *et al.*^[12,13] Under dosages can lead to inappropriate management of the patients as there is no scientific basis or evidence for it.^[14]

The risk of occurrence of adverse events associated with the use of off-label use is 1.6 times greater than for non-off-label use. Adverse events cannot be attributed definitely to off-label use, and the observed increase in adverse events (odds ratio 1.6) is an association, not a causation. Study by Horen *et al.* at France in 2000–2001 in paediatric outpatients reported a 3.44 times risk of adverse events with off-label use of drugs.^[15] The adverse events that could be possibly attributed to off-label use were nausea and vomiting, sedation, etc.

In our study, 92% of paediatric patients were prescribed at least one off-label drug. Furthermore, anaesthesia delivery among paediatric patients is no longer confined to the operation theatres and Intensive Care Units but is also being increasingly used in the non-surgical settings such as long diagnostic procedures, radiological and interventional studies, to allay pain and anxiety and to maintain stable vitals.^[16]

Among the most commonly prescribed drugs as off-label in this study, ramosetron was prescribed off-label for inappropriate indication in 116 patients. Unavailability in hospital formulary increases the

surgical cost.^[17] Due to equivalent efficacy of both ondansetron and ramosetron, the cheaper alternative ondansetron remained a better choice in our set up. Moreover, there was an observational study of ramosetron in progress in the hospital during the study. However, there was no selection bias regarding inclusion of all or many cases where ramosetron was used which would have increased the total number of off-label drug usage.

Buprenorphine-approved dose is 300–450 µg for perioperative analgesia, but it was used in off-label manner at a lower dose, that is, 150 µg in all cases. (32 occasions by IV route and 2 by epidural route) Moreover, buprenorphine has been found to be a potent analgesic at a dose of 0.3 mg by oral route.^[18] Anaesthesiologists might have used this lower dose considering the body mass index of Indian patients.

The other drug which we found used as off-label was fentanyl. It is approved only for intravenous use for perioperative analgesia, but in 25 cases it was used by epidural route. In spite of safety constraints such as hypotension, nausea, vomiting and pruritus, in some cases, its well-proven efficacy and safety makes its use clinically justifiable.

There is ample evidence suggesting that propofol use in children for sedation is associated with minor adverse events that can be easily managed under expert supervision. However, the fact lies that this sedation is only for minor procedures with minimal intervention. Even though majority of the studies focus on overall paediatric population, the risk is more in children less than three years of age.^[19] Propofol was prescribed off label in children on 27 occasions. This was not specific for propofol but use off label drug usage was also greater in paediatric surgery department as compared to other two departments. Cost and logistic considerations, small market share and ethical issues due to vulnerability of paediatric population are the cruxes of lack of enthusiasm in pharmaceutical industry to conduct clinical trials in children enhancing off-label use.^[20]

The latest FDA guidelines regarding off-label drug use allow companies to distribute texts and peer-reviewed scientific articles describing off-label use to physicians which are subject to new regulations.^[21] Indian Medical Association is of the view that off-label drug use is imperative for certain conditions and should be left at the discretion of physician.^[22]

If off-label drug use is based on sound scientific evidence, accurate clinical judgement and practiced in the best of patients' interest, then it can be considered as neither illegal nor unethical. However, the sole responsibility of the off-label prescription here lies with the prescriber.

The prescriber in our study is the anaesthetist who works in a critical care setup, where already the risk involved and chances of morbidity and mortality are quite high.

A detailed analysis of the cause of complications related to off-label use of drugs has not been carried out, which was a limitation of the study. No formal randomisation was done during selection of patients. Furthermore, a causality (relatedness) assessment was not performed for adverse events.

CONCLUSION

Investigation into the off-label use of medications in anaesthesia in surgical wards revealed that such use was practiced in anaesthesia department with questionable clinical justification in some instances.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Announcement

CALENDAR OF EVENTS OF ISA - 2015

Certain important dates are given here for the members. All the applications should be sent by registered post (with Acknowledgement Due)

Date	Name of the Award/Post	Application has to be sent to
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15 th August 2015	Prof. A. P. Singhal Life Time Achievement Award	Hony. Secretary, ISA
31 st October 2015	Dr. (Mrs.) Rukmini Pandit Award - Publication format along with Conference Presentation Certificate	Hony. Secretary, ISA
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31 st October 2015	Dr. Kop's Award	Chairman Scientific committee of ISACON with a copy to Hony Secretary ISA
27 th November 2015	Dr. TN Jha Memorial & Dr. KP Chansoriya Travel grant	Hony. Secretary, ISA
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	2. Best State Branch	
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