Pharmacovigilance Among Surgeons and in Surgical Wards: Overlooked or Axiomatic?

Gabriel Sunil Rodrigues · Sohil Ahmed Khan

Received: 22 July 2010 / Accepted: 17 November 2010 / Published online: 1 December 2010
© Association of Surgeons of India 2010

Abstract To review the status of pharmacovigilance system among surgeons and in surgical wards with recommendations. Literature search using MEDLINE, cross-reference of published data and review of World Health Organization—Pharmacovigilance transcripts. Pharmacovigilance system is still in its infancy among surgeons and in surgical wards. No major studies have been published addressing this issue, till date. Surgeons are professionals least likely to report adverse drug reactions. Moreover widespread and irrational antibiotic use is contributing towards high incidence of adverse events apart from multidrug resistance. Lack of interest, funding and knowledge pose challenges in effective post marketing drug surveillance in surgery. A three tier proactive pharmacovigilance system in surgical wards is suggested along with specific recommendations. The pros and cons of adverse drug reporting among the surgeons are discussed. With growing awareness of pharmacovigilance in various fields of medicine, surgery can no longer remain an exception. In the transition from medical school to surgery clinic a subtle shift must occur from emphasizing pharmacokinetics to appreciating pharmacodynamics. This change in philosophy will occur at the level of instruction when the

surgeons of tomorrow are motivated through regulatory and institutional means at school level to adopt pharmacovigilance in their clinical practices along with the practicing surgeons.

Keywords Pharmacovigilance · Pharmacodynamics · Adverse drug reactions · Surgery

Introduction

Evolution of pharmacovigilance in recent years and its growing importance as a science critical to effective clinical practice is increasingly and constantly felt by healthcare fraternity and regulatory bodies. Pharmacovigilance is the science relating to the detection, assessment, understanding and prevention of adverse effects or any possible drug related problems [1]. Recently, its concern has been widened to include herbals, traditional and complementary medicines, blood products, biologicals, medical devices and vaccines. The specific aims of pharmacovigilance are to improve patient care and safety in relation to the use of medicines and all medical and paramedical interventions, improve public health and safety in relation to the use of medicines, contribute to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost-effective) use, and promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public. Drug safety constitutes the cornerstone of modern therapeutics. Nowadays, the focus tends to be more on the hazards of drugs rather than on their benefits. The medical team of World Health Organization (WHO) aims to assure safety of medicines by ensuring reliable and timely exchange of information on drug safety issues, promoting pharmacovigilance activities throughout the

G. S. Rodrigues (✉)
Department of General Surgery, Kasturba Medical College,
Manipal University,
Manipal 576 104 Karnataka, India
e-mail: rodricksgaby@yahoo.co.in
e-mail: gabyrodricks@gmail.com

S. A. Khan
Department of Pharmacy Practice, Manipal College
of Pharmaceutical Sciences, Manipal University,
Manipal, Karnataka, India

organization and encouraging participation in the WHO programmes for International Drug Monitoring. Initiation of Uppsala monitoring centre by WHO facilitates the management of international database of adverse drug reactions (ADRs) received from the national centers for active surveillance on drug safety worldwide [2].

Pharmacovigilance in Surgery

Drug therapy is an integral part of surgery and cannot be overlooked. Rapid progress in pharmacotherapeutics mandates that surgeons constantly update their knowledge of new drugs, drug safety and therapeutic trends. An increase in the incidence of drug disasters stresses the need for vigilance in spontaneous reporting of adverse events by surgeons. A shadow of uncertainty and confusion still persists when it comes to effective working of pharmacovigilance system in specialties like surgery that can prove hazardous. Medical misadventures like medication error are very common in surgical wards. A wide range of drug class is prescribed by surgeons and antibiotics comprise the majority of them and irrational antibiotic usage is a common problem leading to emergence of multidrug resistance organisms and high incidence of adverse reactions. Surgeons come across numerous drug induced severe dermatological reactions but still it is observed that surgeons are the professionals least likely to report ADRs [3]. The problem becomes more severe when newer antibiotics and other drugs are launched in the market. Causal association between the drug and reaction is very important to prevent future drug disasters. Spontaneous reports from surgeons are vital in the current situation because clusters of case reports that suggest an adverse reaction are frequently the first and only signal that could predict such a problem. There are numerous challenges for effective pharmacovigilance functioning in surgery. Post marketing surveillance and randomized trials is a rarity in the field because of lack of funding, costs, small sample size and lack of interest from the industry. Surgeon's knowledge on clinical epidemiology and data collection remains poor. Standard randomized controlled clinical trials comparing medical treatments in surgical patients' accounts for 75% of surgical trials [4]. Among these, the typical phase three trials deal with several thousand patients that can often be fewer than a thousand in surgery. This means that ADRs that occur in fewer than 1 per 1000 patients may be missed and can only be recognized subsequent to market approval of a drug [5]. Lack of confirmatory evidence for newer ADRs can prove fatal in future course. The greater the experience with the drug through clinical trials or clinical use, the greater the understanding of risk will be. Hence baseline reporting by surgeons is crucial. Other important reasons for a proactive approach in post marketing ADR monitoring are: (1) tests in

animals are insufficient to predict human safety, (2) patients under clinical trials are selective and limited in number, (3) the duration of trials is short, (4) exposure of less than 5000 human subjects (fewer than a thousand in surgery) to a drug allows only the more common ADR to be detected. At least 30,000 people need to be treated with a drug to be sure that one does not miss at least one patient with an ADR which has an incidence of 1 in 10,000 exposed individuals and (4) information about rare but serious adverse reactions, chronic toxicity, and use in special groups (such as children, the elderly or pregnant women) or drug interactions is often incomplete or not available. Clinical trials may be a better test of efficacy than are of safety under practical conditions of everyday clinical usage. Another reason is that clinicians may be slow or passive in detecting and reporting ADRs in such situations [6]. Moreover the proactive approach in ADR reporting becomes more important for newer agents in surgical therapeutics.

Methods to Promote a Culture of Safe Drug Usage

At the stage of initial identification of ADRs it is almost never sure whether the hazard is drug related or not and this has led to the concept of 'signaling'. A signal is an alert from many available sources that a drug may be associated with a previously unrecognized hazard or that a known hazard may be quantitatively (e.g. more frequent) or qualitatively (e.g. more serious) different from existing knowledge. Spontaneous ADR reporting is the classic signaling system. Three cases may be considered a signal and five cases a strong signal. Once a signal has been identified from any source, the next step is to perform an assessment and includes reviewing the strength of the evidence that indicates a possible drug related hazard and the consideration of other immediately available evidence which may help to support or oppose the hypothesis. The nature of action taken will depend on several factors that include seriousness of the hazard, frequency, preventability, nature of the disease, benefits of treatment and availability of alternative treatments. Dose and duration of treatment often are important [7]. An example in surgery would be to limit the duration of prophylactic antibiotic preferably to three days postoperatively with evidence of fever and microbial culture. The timing of how quickly information needs to be made available to users is critical. Life threatening ADRs need prompt intervention whereas mild ones like nausea can be taken into consideration in next routine labeling revision. Current system of ADR management relies heavily on statistical evaluation of signal and mathematical quantification of risk within the exposed. Pharmacogenetics can play a specific role in targeting the risk of occurrence of ADRs in particular population through genetic mapping but it has a long

way to go. Till then, risk communication plays an important role in prevention and management of ADRs that should be accurate, balanced, open, understandable and targeted.

Building an Effective Pharmacovigilance System in Surgery

A three tier approach is important for building a proactive pharmacovigilance system (Fig. 1). A strong regulatory framework with organizational support is important for introduction and implementation of a robust pharmacovigilance program at a national level in surgery. Surgical school can collaborate and integrate organizational approach to patient safety through initiation of a surgical safety team at an institutional level. A surgical safety team may be a stand alone-entity that reports directly to the institution's board of directors or surgery board or it may be a subcommittee of a larger group like patient safety committee or a pharmacy and therapeutic committee [8]. Practicing surgeons and residents need to receive adequate training about the local surveillance system of ADR reporting with respect to why

and for what it exists. Knowledge deficits exist in the surgical community on the role of food and drug administration (FDA) and local Institutional Review Boards (IRBs) for conducting clinical trials that can act as a barrier in smooth functioning of pharmacovigilance system [9]. At the baseline, individual surgeons need to be trained in pharmacovigilance programs and horizontal communication between other healthcare professionals is crucial. Pharmacology classes must emphasize the limitations of clinical trials in evaluation an ADR and need to continue drug evaluation in post licensing period. Collaboration with departments like clinical pharmacology and clinical pharmacy can play a key role in medication safety management measures. ADRs in surgery may be reported and collected from spontaneous reporting systems maintained by the Food and Drug Administration (FDA) Medwatch (www.fda.gov/medwatch/index.html) and the WHO spontaneous reporting database (www.who-umc.org) apart from the institutional reporting system. Surgeons need to know how to recognize, report an ADR and to evaluate the outcome of pharmacovigilance program [10, 11]. The snapshot is tabulated under Table 1.

Fig. 1 Three-tier pharmacovigilance system in surgery wards

Table 1 Pharmacovigilance: a snapshot on what surgeons need to know?**How to recognize an ADR?**

Determine the time interval between the drug administration and onset of reaction; evaluate the suspected ADR after discontinuing the drug or reducing the dose; if appropriate, restart the drug treatment and monitor the recurrence of any adverse events; analysis of alternative causes; use relevant evidence based literature and clinical experience on drug usage and verify previous conclusive reports on this reaction. Report any suspected ADR to the person nominated for ADR reporting in the hospital or directly to the National ADR Reporting Centre.

What to report?

For new drugs—report all suspected reactions, including minor ones; For established or well-known drugs—report all serious or unexpected suspected ADRs; If an increased frequency of a given reaction is observed; In special fields of interest such as drug abuse and drug use in pregnancy and during lactation; When suspected ADRs are associated with drug withdrawals; ADRs occurring from overdose or medication error; When there is a lack of efficacy or when suspected pharmaceutical defects are observed.

How to measure the outcome of pharmacovigilance program?

Medication safety data can be used to measure how changes has modified the medication use process and affected the potential for patient harm.

Process measurements: Percentage of staff completing training in medication safety, pharmacist intervention per 100 admissions, number of self-reported medication errors and number of potential or near-miss medication errors with high-alert drugs.

Outcome measurements: Percentage of emergency department visits caused by adverse drug events, number of preventable adverse drug events per 1,000 doses, average length of stay for a patient experiencing an adverse drug event, severity of adverse drug event and patient satisfaction scores.

The Other Side of the Story: Problems in Reporting Events

When it is necessary and important to report ADRs, severe deficiencies in the culture of reporting adverse events is also evident. Firstly there seems to be a difficulty in navigating the bureaucracy and then an additional workload of submitting an ADR report on surgeons. The filled in forms/reports are often incomplete and lack important data pertaining to the duration and dose of the drug to establish a causal relationship. Biriell and Edwards [12] in their pilot study have indicated Inman's 'seven deadly sins' that influence reporting of an ADR (Table 2). There is a need to address those factors through educational programs. The concept of generating a signal from ADRs is useful only if the signal is taken seriously and the action taken is prompt and proportional to the strength of the signal. Surgeons desire to receive

feedback from the pharmacovigilance system about the report they have submitted and the current system lacks a two way interaction. The bane of pharmacovigilance today in surgery remains that drug companies continue to invest large sums of money in promotional launches than commit a proportion of their funds to propagating training and awareness programs that would promote early reporting of ADRs. Proactive participation of other healthcare professionals in general and surgeons in particular is required for increasing and updating the awareness of pharmacovigilance in surgical practice.

Conclusion

With growing awareness of pharmacovigilance in various fields of medicine, surgery can no longer remain an exception. In the transition from surgery school to surgery clinic a subtle shift must occur from emphasizing pharmacokinetics to appreciating pharmacodynamics. This change in philosophy will occur at the level of instruction when the surgeons of tomorrow are motivated at school level to adopt pharmacovigilance in their surgical practices. If the industry/regulatory bodies expect surgeons to report adverse drug events then they must be sensitized to understand the benefit of doing so to the practice of the specialty as a whole. Early and more thorough reporting of ADRs will directly influence the speed with which drugs can be withdrawn; this has a direct impact on the lives of patients who would otherwise have consumed the problematic drug.

Table 2 Inman's 'seven deadly sins' of reporting adverse drug reactions

Fear: Of litigation

Indifference: About contributing to the general advancement of knowledge

Ambition: To collect and publish a personal case series

Guilt: At having caused an adverse effect

Complacency: The mistaken belief that only safe drugs are licensed

Ignorance: Of the need for reporting

Diffidence: About reporting a mere suspicion

Conflict of interest None

Source of funding Nil

References

1. Mann RD, Andrews EB (2002) Introduction. In: Mann RD, Andrews EB (eds) *Pharmacovigilance*. Wiley, London, pp 3–5
2. WHO Programme for International Drug Monitoring. Available from URL: www.who-umc.org on 29th November 2009
3. Sam P, Gordon T (2007) Doctors with a problem drug. *Student BMJ* 15. Available from www.studentbmj.com on 29th November 2009
4. Peter M, Irving T, Mitsuru S et al (2002) Randomized trials in surgery: problems and possible solutions. *BMJ* 324:1448–1451
5. Joan WM (2006) Using a drug before the risks and benefits are known from a phase 3 clinical trial. *Arch Ophthalmol* 124:1029–1031
6. Khan SA, Rao PG, Rodrigues GS et al (2006) From Thalidomide to Rofecoxib: can we afford to wait and watch? *Int J Risk and Safety in Med* 18:219–230
7. Waller PC, Tilson HH (2004) Managing drug safety issues with marketed products. In: Talbot J, Waller P (eds) *Stephen's detection of new adverse drug reactions*. Wiley, London, pp 345–374
8. May S (2005) Building an effective medication safety team. In: Manasse HR, Thompson KK (eds) *Medication safety: a guide for health care facilities*. American Society of Health-System Pharmacists, Maryland, pp 89–106
9. Randi LR, Edwin AD, Paul W (1997) Academic surgeons' knowledge of food and drug administration regulations for clinical trials. *Arch Surg* 132:94–98
10. Safety of Medicines: a guide to detecting and reporting adverse drug reactions. Available from: whqlibdoc.who.int/hq/2002/WHO_EDM_QSM_2002.2.pdf on 29th November 2009
11. Institute for Health Care Improvement and BMJ Publishing Group. Medication Systems—Measures. Available from: www.qualityhealthcare.org/QHC/Topics/PatientSafety/MedicationSystems/Measures on 29th November 2009
12. Biriell C, Edwards IR (1997) Reasons for reporting adverse drug reactions—some thoughts based on an international review. *Pharmacoepidemiol Drug Saf* 6:21–26