Editorial

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Pharmaco-genomics and anaesthesia: Mysteries, correlations and facts

Clinical importance of genetic disorders is being increasingly recognised in anaesthesia practice as more number of cases present for surgeries in our country, evidenced by submissions and publications in this journal.[1] Much of this is the result of newer diagnostic modalities, increased awareness and advanced genetics.[2,3]

Some of the genetic disorders are incidentally detected during pre-anaesthetic evaluation while some are pre-diagnosed; the challenges become manifold during emergency surgeries due to inadequate time for evaluation and optimization.[2]

Genetic disorders may manifest as abnormalities and derangements involving different organ systems which have been comprehensively described in a systematic review by Butler *et al*.[2] The presence of neurological and developmental defects is difficult to diagnose as most of the patients are young and specialist assessment could be needed. Impairment of vision and hearing compounds the problem.[2]

Since the range of disorders is so varied, management guidelines have evolved only for some of the more recognised disorders such as malignant hyperthermia, porphyrias, α-thalassemia, Down's syndrome and other congenital disorders while rest are managed purely on case by case basis.

The genetic disorders may be autosomal dominant, recessive, X-linked, homozygous or heterozygous in presentation. Genes which undergo mutation when subjected to volatile anaesthetics have been identified in experimental animals such as mice, flies and worms (Syntoxin, Stomatin, Gas-1, White/brown Drosophila genes, Para genes, etc); they can impact cell function and the response to anaesthetics.[4] Mutations of the genes which code for the subunit of GABA receptors in brain can account for increased anaesthetic requirement as the resistance to volatile anaesthetics increases, possibly contributing to individual variations in response to anaesthetic drugs.[4]

The study of such differences in response to certain drugs among individuals constitutes the speciality of pharmacogenomics. The pharmacogenomics have been able to exert a considerable influence on anaesthetic and surgical outcome thereby decreasing the peri-operative anaesthesia morbidity.[4]

Studies in mice show that resistance to hypnotic effects of nitrous oxide, sedative and hypnotic effects of propofol and etomidate are associated with mutations involving subunits of NMDA and $GABA_A$ receptors.[5-8] Dexmedetomidine can show a variable vasoconstrictor response in individuals with a genetic homozygous variation at AR-alpha-2BD allele.[9] Patients with a variant of SLCO1B1 gene are highly vulnerable to statins induced rhabdomyolysis.[10] Studies have related genetic basis to adverse outcomes such as angina, arrhythmias, myocardial infarction (MI), bleeding, cognitive dysfunction, renal dysfunction, etc.[11] Genetic polymorphism can be held responsible for a variable coagulation activity during a peri-op period such as fibrinolytic activity and tissue plasminogen activator inhibitor.[12,13] Genetic predisposition with alterations in TNF-α and interleukin-8 levels can be associated with sepsis and inflammatory response to exogenous stimuli.[14]

In one of the investigations published in the present issue, the authors checked for possible divergence in onset of sedation using propofol and midazolam based on Bispectral index (BIS) and Observer's Assessment of Alertness/Sedation (OAA/S) scores in patients undergoing

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infra-umbilical surgeries under subarachnoid block. There was greater divergence in time to reach a target BIS score of 70 and an OAA/S score of 3 when midazolam was used when compared to propofol. If the patient is more anxious, it is possible that the time to suppress the cerebral activity could be prolonged, contributing to the observed delay in the decrease in BIS scores in patients sedated with midazolam despite the patient being clinically asleep.[1] Genetic and pharmacology correlations for this finding should be ideally attempted at the cellular level, with larger sample size in order to make the findings more authentic.

The ability to adjust to the insults resulting from genetic variations is also different among individuals.[15] The degree of such 'variations' also differs among various population groups and explains the differences in prevalence in these groups; ethno-pharmacy as a subspecialty is gaining importance.

Genetic variations and impact on metabolic enzymes

Genetic variations may influence the activity of hepatic enzymes CYP2D6 which influences many pharmacological activities during peri-op period. Gene expression resulting in enhanced CYP2D6 activity can cause increased conversion of codeine to morphine resulting in higher incidence of opioid-related side effects and vice versa. The enhanced metabolic activity of CYP2D6 results in increased metabolic turnover of 5HT3 antagonists like ondansetron and a consequent higher incidence of PONV.[16] Genetic variations in the μ-receptors caused by G variant of OPRM1304 receptor can lead to exaggerated effects of intrathecally administered fentanyl.[17] Genetic variations in the hepatic enzyme CYP3A4 can lead to variable response to routinely used drugs such as benzodiazepines, opioids, steroids and 5HT3 antagonists.[3]

Further research and evidence of pharmacogenomics in anaesthesiology is needed to pin-point clear associations between genetics, inter-personal and intra-personal variations in response to the various anaesthetic agents that can act as practice guidelines.

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