Editorial II

Why does smoking protect against PONV?

Postoperative nausea and vomiting (PONV) are among the most common and feared postoperative complications and can occur after both general and regional anaesthesia. Many adults find PONV more distressing than postoperative pain.[1] Over the last decade, there has been some improvement in the understanding of the aetiology, and pathophysiology of PONV and, together with the introduction of new and effective antiemetics there has been some progress into finding a solution to the problem. Unfortunately, however, PONV, which has been described by Kapur as 'the big, little problem',[2] remains an unpleasant and sometimes intractable side-effect, which continues to challenge and frustrate anaesthetists. In today's world of cost-effective medicine, where there are ever-increasing pressures to avoid even minor side-effects of treatment, there has been an explosion of papers on the subject in which every aspect of risk, prevention, anaesthetic technique, and management strategies have been examined. PONV has also been the subject of a recent 1-day symposium organized by The Royal College of Anaesthetists.[3]

Several authors have attempted to categorize PONV in terms of surgical, anaesthetic, non-anaesthetic, and post-operative factors.[4 5] A number of factors have emerged which are associated with the problem. These include age, sex, history of motion sickness, previous PONV, duration and type of surgery, pre-anaesthetic medication, the use of nitrous oxide, facemask ventilation, the use of opiates, early postoperative ambulation, the timing of oral intake, and postoperative pain. Clearly, there are an infinite number of permutations that may lead to an unfavourable outcome. For this reason, there have been attempts to define those variables and in particular, those fixed patient factors that may be used to quantify more meaningfully the extent to which an individual may be at risk. It is also important to take cognisance of these factors in the design of studies of PONV in order to avoid bias. In 1993, Palazzo and Evans[6] studied prospectively 147 patients undergoing minor orthopaedic surgery, by logistic regression analysis, to determine the association of independent fixed patient factors with the incidence of PONV. This study identified history of PONV, sex, and postoperative opioid administration as important

factors. A history of motion sickness was weakly associated. There was also an interaction between sex and history of motion sickness. In 1998, Apfel and co-workers,[7] also using stepwise forward logistic regression analysis analysed 1137 patients and identified age, sex, history of PONV or motion sickness, duration of surgery, and *non-smoking* as important risk factors in the aetiology of PONV. Simultaneously, Hough[8] coincidentally identified smoking as a protective factor against PONV. This was confirmed by Chimbira[9] in a larger follow-up study.

Why should cigarette smoking confer protection against PONV? One explanation for such an effect would be the presence of an antiemetic substance in tobacco smoke. The pharmacological receptors which mediate PONV are known to act at the dopamine (D2), cholinergic, histamine (H1), 5-HT3 and NK1 receptors,[10] and if there were an antemetic in cigarette smoke it would have to belong to one of these classes of receptor-blocking drugs. Presumably, if this were the case, then other dopaminergic, cholinergic, or histaminergic effects would occasionally be seen. So far this hypothesis has not borne fruit. Alternatively, the reduction in PONV may be seen as an adaptive response to a repeated emetic stimulus, although it is clear that usually only the uninitiated or those who have consumed excessive amounts find tobacco emetogenic.

Cigarette smoke is a complex mixture of gaseous and particulate material. The gaseous portion, which comprises 60% of tobacco smoke, contains formaldehyde, carbon monoxide, nitric oxide, hydrogen cyanide, and other components.[11] The remaining 40% is the particulate phase. There are about 3500 different substances, which have been isolated in the particulate phase, the principal one of which is the alkaloid, nicotine. Other alkaloids include nornicotine, antabine, and anabasine. There are also acids, including lactones, aldehydes, ketones, alcohols, polyphenols, nitrosamines, and polyaromatic hydrocarbons.[12] The particulate phase minus the alkaloids and water is called tar.

Tar, otherwise known as cigarette smoke condensate (CSC), is a mixture of polycyclic aromatic hydrocarbons (PAHs), *N*-nitrosamines, and aromatic amines.[13] PAHs are the products of incomplete combustion of organic matter such as wood, oil, tobacco, and coal. In recent years, research has focussed to a large extent on these substances, primarily because of their tumorigenic activity and also because they are capable of influencing the activity of hepatocellular enzymes.[14] Examples of the PAHs, which are found in CSC include naphthalene, phenanthrene, anthracene, benzanthracene, pyrene, benzpyrene, and benzfluoranthene.

Detoxification of most drugs occurs via the P450 (CYP) enzyme pathways. In man, the CYP isoenzymes, which are responsible for drug metabolism belong to families 1–4. Of these families, 1–3 are the most important. It has been estimated that 90% of drug and xenobiotic metabolism can be attributed to six enzymes: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4.[15] The purpose of this multienzyme system, which has evolved over millennia in plants and animals, is an evolutionary consequence of plant–animal warfare. Plants synthesized chemicals for self-protection, and animals had to develop xenobiotic-metabolizing enzymes such as cytochrome P450 for the detoxication of these chemicals.[16] It can now be considered as an adaptive response to environmental challenges, in that exposure to a toxic or noxious substance results in the expression of enzymes responsible for the metabolism of the particular toxin. For the most part this is a beneficial response, but it may also result in the formation of a metabolite that is either pharmacologically active or even carcinogenic.[17] When enzymes are induced, dramatic effects on drug clearance and half-life can also occur.

Cigarette smoking can result in as much as a 3-fold increase in CYP1A2 activity from induction by PAHs. CYP1A2 is the major enzyme involved in the metabolism of a number of drugs, some of which are commonly used by anaesthetists. This leads to increased rates of metabolism of these substances, which may lead to an increased dosage requirement.[15] For example, it has been shown that the clearance of theophylline is significantly increased in smokers and that its half-life is decreased by a factor of two.[18] Cessation of smoking can lead to rapid accumulation which necessitates dose readjustment.[19] The metabolism of a number of psychoactive drugs also dependent on CYP1A2 is similarly affected. These include the antidepressives amitriptyline, clomipramine and fluvoxamine, the antipsychotics chlorpromazine and haloperidol, and some anxiolytics such as diazepam and chlordiazepoxide.[20] Of interest to anaesthetists is the increased requirements for analgesia among smokers and the increased metabolism of morphine and meperidine.[21 22] Pentazocine and dextropropoxyphene which are associated with the genesis of PONV may be similarly affected.[23 24]

In contrast, volatile anaesthetics are metabolized by CYP2E1,[25–27] which is also induced by nicotine and PAHs.[18] In a recent study, Apfel and co-workers[28] have demonstrated that volatile anaesthetics are the main cause of PONV within the first two postoperative hours, when pharmacokinetic effects are most likely to account for any perceived differences in recovery. A patient whose liver enzymes, in particular CYP2E1, have been induced as a result of smoking would be expected to have a correspondingly higher rate of metabolism of the respective volatile agent. Such a patient might have a quicker and smoother recovery from anaesthesia.

Our understanding of liver enzymes and how they may be influenced by foreign substances has improved considerably over the last decade and has been the subject of several reviews.[29 30] Liver enzymes are induced or inhibited by a number of commonly used drugs, environmental chemicals, for example insecticides, petroleum products and solvents, as well as foodstuffs, which may therefore interfere with recovery from anaesthesia.

There are a number of well-known serious pharmacological interactions, which occur as a result of P450 inhibition. For example, cimetidine, which is a non-specific inhibitor of several CYP isoenzymes, can interfere with the breakdown of a number of substances including non-depolarizing muscle relaxants,[31] and warfarin,[32] leading to prolonged paralysis and excessive anticoagulation respectively. Another potentially fatal interaction, caused by a cardiac dysrhythmia, is that involving the macrolide antibiotic, erythromycin, which inhibits CYP3A4, and the commonly used antihistamine, terfenadine.[33] The combined use of these two substances can lead to prolongation of the QT interval thereby triggering a specific arrhythmia known as *torsade de pointes*. An identical problem results when excessive amounts of grapefruit juice are consumed while taking terfenadine.[34] Grapefruit juice is known to contain the bioflavanoid, naringin. These bioflavanoids are a group of naturally occurring substances which are thought to be responsible for inhibiting CYP3A4,[35] which is also responsible for metabolizing benzodiazepines and opioids such as alfentanil.[15] Of interest has been the recognition of the ability of these substances also to block enzymes of the CYP2 family.[36] On the other hand, cruciferous vegetables such as cabbage, brussel sprouts, and cauliflower, contain indole-3-carbinole which is a potent inducer of CYP1A2,[37] but they also contain phenethyl isothiocyanate which is an inhibitor of CYP2E1.[16] Another inhibitor of CYP2E1 is dihydrocapsaicin which is found in red peppers.[38] A subject undergoing anaesthesia having recently consumed large amounts of this substance may have an unexpectedly long recovery and if also a smoker may lose his protection against PONV.

Alcohol intake before an anaesthetic is also a hitherto underestimated factor, which probably is as important as tobacco in determining the risk of PONV. Not only is alcohol a potent inducer of CYP2E1, significant increases in the enzyme appearing after only a single ingestion,[38] but there is a curious synergy between alcohol and tobacco. The incidence of alcoholism is 10 times more likely in smokers[39] consistent with the concept that smoking increases ethanol consumption.[40] It would be interesting to speculate that hitherto disregarded patient factor for PONV might be dietary preference and alcohol intake on the evening before surgery.

Liver enzyme status may be subject to genetic polymorphism, with the expression of a number of liver enzymes being dependent on factors such as sex and racial differences. For example, the activity of CYP2D6 (debrisoquine 4-hydroxylase) which is responsible for the metabolism of many drugs, including some opiates, such as codeine,[15 30] which are known to cause PONV, varies widely along racial lines. The prevalence of the poor metabolizer approaches 10% among Caucasians but is virtually zero in Japanese subjects.[41] The breakdown of nicotine is determined by the level of CYP2A6 (coumarin-7-hydroxylase), the activity of which is also determined to some extent by genetic background.[42] CYP2E1 may also be subject to genetic polymorphism,[43] which could explain interindividual differences in the tolerance to anaesthetic agents. Finally, an interesting cause of CYP2E1 induction is obesity,[44] which might also therefore confer resistance to PONV. It might explain the association between halothane hepatitis and obesity,[45] which is known to occur as a result of a reaction to a trifluoroacetyl metabolite of halothane.[46]

In summary, enzyme induction is an important mechanism that may influence the breakdown of a number of volatile and non-volatile anaesthetic agents. The extent to which liver enzymes are induced will determine the rate and possibly the quality of recovery. There are interindividual, racial, and sex-related differences in the activity of liver enzymes including CYP2E1, and this could explain some of the differences in recovery from anaesthesia. There are a number of pharmacological, dietary, and environmental substances including cigarette smoke that can induce or inhibit CYP1A2 and CYP2E1. The way in which an individual responds to an anaesthetic will depend on a subtle interaction of his or her genotype together with these exogenous factors. A novel approach to improving outcome after anaesthesia may be by targeting enzymes pre-emptively with specific inducers to alter their activity and thereby mimic the apparent advantage of the smoker without running the other risks to which he is exposed.

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