INTRODUCTION

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Definition of Anaesthetic Toxicity

Definitions are difficult and never entirely satisfactory. Certainly, toxicity can be defined as any adverse functional or structural change in an organ or functional system, due to the direct effect of a chemical or biological product which is inhaled, ingested, injected or absorbed, or which yields metabolites with an identifiable adverse effect on the organ or functional system. Even this does not encompass the whole picture. The degree of toxicity is of practical clinical consequence, as is the reversibility or irreversibility and the incidence of occurrence.

Toxic effects of anaesthetics are relatively rare. The safety margin, though, can be uncomfortably small. This is particularly well demonstrated with respect to the local anaesthetic agents.

The Cell and Anaesthetic Toxicity

The cell must surely become the starting point for an understanding of toxicity and this will become clear from many of the remarks of the participants in this symposium. During anaesthesia, in the broadest and simplest sense, the cell milieu (intracellular and/or cell membrane component) is somehow altered reversibly so that there is inhibition of the normal function of that cell. Studies of the cell are better undertaken in the experimental preparation, where more precise information on kinetics and efflux can be presented under clinical simulation. But it will be much more meaningful to the clinician if anaesthetic levels used in experimental models are within clinical ranges and expressed in the same units as those used in administering the drugs to patients. This is not always done.

Another aspect, now apparent, is that anaesthetic agents may affect a series of receptor sites in the cell. Narcosis may only be one of several cellular effects of anaesthetics. Others include decreased contractile force, inhibition or induction of metabolism, interference with mitosis and teratogenicity. These features will become apparent during the discussions presented in this symposium.

The Organ or Functional System and Toxicity

Some gross sites appear more vulnerable and more easily identifiable than others in relationship to toxicity. This is a fact dependent upon a variety of factors.

- (1) *Organ perfusion and circulation dependency factor:* In richly perfused organs, for instance kidney and liver, more anaesthetic will reach a site of action or concentration than in less richly perfused tissues. These same structures may also be more vulnerable to decreased perfusion. It is worth remembering that a surgical procedure may significantly jeopardize organ perfusion, resulting in structural hyponutritional damage, entirely independent of anaesthesia.

- (2) *Structural-functional make-up of an organ*: The structure and function of an organ may be conducive to the amassing of high concentrations of an anaesthetic agent or its toxic metabolites, as in the case of fluorides in the kidney, or it may have access to mechanisms for producing by-products of the anaesthetic agent, as in the liver and enzymatic cytoplasmic membrane and endoplasmic reticulum activity.
- (3) *Metabolic rate of an organ*: There is a greater susceptibility to cellular anoxia in an organ of higher metabolic rate, during an impaired phase.
- (4) *Interorgan dependency*: A change in function of one organ produced by an anaesthetic may be due to the anaesthetic effects on cardiovascular function, sympathetic nervous system activity or endocrine function.
- (5) *Functional base-line of the patient*: The acid/base electrolyte and fluid balance status of the patient will alter susceptibility to the toxicity of anaesthetic agents.

It becomes apparent that not all factors influencing toxicity are direct and primary, but that indirect secondary features cannot be ignored as important contributing factors in the toxicity problem.

The Anaesthetic Agent as Causative Toxic Factor

By classical definition a direct toxic effect of an anaesthetic agent could be assumed if there was organ damage of a distinct histological pattern, which appeared after a predictable and usually brief latent period following exposure to the offending agent; if the damage was elicited in all exposed individuals and could be reproduced in experimental animals; and if the damage was dose related.

We can no longer be entirely complacent about such criteria. More sophisticated mechanisms are now known to be operational. Even dose-concentration relationship concepts are now challenged, in certain instances, in light of the recently demonstrated concentration dependence phenomenon of halothane, reviewed in this symposium. Further, the concept of biotransformation and the importance of the biodegraded products of an anaesthetic agent have become well documented, as in the case of inorganic fluoride and oxalic acid from methoxyflurane and their relation to alterations in kidney. These are reviewed thoroughly in this symposium. Individual variation in sensitivity or hypersensitivity to these products and anaesthetic agents can be great. In addition, we are just beginning to assess and to be aware of the influence of such factors such as enzyme induction, the significance of repetitive use phenomena and the widespread problem of interaction of drugs.

CORRELATION is not always proof of CAUSATION. Steps between observation, interpretation and conclusions can become emotionally entangled. The following anecdote will serve to illustrate this point.

A knowledgeable group of eminent scientists gathered to study the behavioural training of jumping fleas. A flea was placed in front of a barrier and was eventually trained to jump over the barrier when a bell rang. When one leg was removed, the flea jumped just as effectively over the barrier, when the bell rang, as when all its legs were intact. When two legs were removed, the flea still made the jump with ease. Even when four legs were removed, one-half of the total eight legs, the flea made the jump, but with difficulty, when the bell rang. Six legs were then removed. The bell rang. The flea strug-

gled and struggled and eventually had to be helped over the barrier by the scientists. Finally, the last leg was removed – the bell rang – the flea was not able to get over the barrier. The scientists gathered around watched this final event with great sobriety and pondered, in depth, the meaning of their experimental observations. Then with unanimity they announced that the flea did not jump over the barrier – because it had become *DEAF!*

Solutions to all these problems will not be forthcoming from this symposium but it will provide some real concerned thought and helpful approaches to our further understanding and improved management of problems associated with Acute and Chronic Toxicity of Anaesthetic Agents.

RÉSUMÉ

Les définitions sont difficiles et jamais satisfaisantes entièrement. Sûrement, la toxicité peut se définir comme étant un changement néfaste fonctionnel ou structural dans un organe ou un système fonctionnel dû à l'effet direct d'un produit chimique ou biologique inhalé, ingéré, injecté ou absorbé, ou qui libère des métabolites produisant des effets identifiables sur l'organe ou le système fonctionnel. Même cette définition n'englobe pas tout le tableau. Le degré de toxicité est d'une conséquence clinique pratique, comme la réversibilité ou l'irréversibilité et le fait de son apparition.

Les effets toxiques des anesthésiques sont relativement rares. La limite de sécurité cependant peut être très étroite. Ceci peut être particulièrement bien démontré en ce qui a trait aux agents anesthésiques locaux.

Par définition classique un effet toxique direct d'un agent anesthésique pourrait être présumé s'il y avait une atteinte d'une façon histologique distincte à un organe, laquelle surviendrait après une période latente habituellement brève et prévisible à la suite d'un contact avec l'agent agresseur ; si le dommage apparaît chez tous les individus exposés et peut être reproduit en expérimentation chez les animaux ; et si le dommage est en relation avec la dose.

Nous ne pouvons plus nous satisfaire entièrement d'un tel critère. Des mécanismes plus sophistiqués sont maintenant connus. Même les concepts s'appuyant sur la relation entre la dose et la concentration sont mis en doute, dans certains cas, à la lumière du phénomène de la dépendance de la concentration de l'halothane récemment démontré, et qui fut étudié dans ce symposium. De plus, le concept de la biotransformation et l'importance des produits de la biodégradation d'un agent anesthésique est maintenant mieux connus, comme c'est le cas du fluore inorganique et de l'acide oxalique du méthoxyflurane et leurs rapports avec les changements du rein. Ceux-ci sont revus entièrement dans ce symposium. La variation de chaque individu en face de la sensibilité ou de l'hypersensibilité à ces produits et aux agents anesthésiques peut être très grande. De plus, nous ne commençons qu'à évaluer et à être au courant de l'influence de certains facteurs comme l'induction des enzymes, la signification du phénomène d'usage à répétition et le problème étendu de l'interaction des drogues.

Les solutions à tous ces problèmes ne viendront pas de ce symposium, mais il fournira des pensées très intéressées et des approches utiles à notre compréhension plus poussée et un meilleur contrôle des problèmes associés à la toxicité aigue et chronique des agents anesthésiques.