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DEVELOPMENTS IN DRUGS USED IN ANÆSTHESIA

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DEVELOPMENTS IN DRUGS USED IN ANAESTHESIA

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PREFACE

This book reflects the proceedings of the Boerhaave Course, "Developments in drugs used in Anaesthesia", held on May 7th and 8th 1981 at Leiden University.

The goal of the organizers of the course was to obtain a better understanding of the pharmacological and clinical applications of the drugs used in the field of Anaesthesiology. In my opinion, there is a constant need for post-graduate teaching not only on a clinical basis, but also in the so-called "basic sciences". This especially applies to anaesthetists.

I would like to express my thanks to the speakers, who were all so kind as to send their manuscripts in time for publishing, and to thank the co-editors of this book, as well as Mr. B.F. Commandeur, from Martinus Nijhoff Publishers for their fruitful co-operation. Last but not least, I would like to thank the secretarial staff of my department for all the work they did arranging for manuscripts to be in the right places at the right times.

Joh. Spierdijk

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THE USE OF H_2 BLOCKERS

T.H. STANLEY

In the last decade a new important histamine receptor, H_2 receptor, has been discovered which has major importance in gastric acid production. In addition, a new drug Cimetidine (Tagamet) which blocks the H_2 receptor has been synthesized. The object of this presentation will be to discuss the possible role of this interesting drug (Cimetidine) before and during operation and possible postoperatively as well.

There is, as many of you know, a disease entity called Mendelson's syndrome which does not occur frequently but when it does can produce severe pulmonary embarrassment and death in anesthetized patients.[1-7] Mendelson's syndrome or pulmonary acid aspiration, as it is more commonly called occurs when gastric contents with a pH of less than 2.5 is aspirated into the lungs. It appears that gastric juice with a pH >2.5 does not produce changes in the lung (which, incidentally, include hemorrhage, edema, and cellular and structural damage and result in hypoxia). It also appears that a critical volume of gastric juice (0.4 ml/kg or <25 ml) as well as a pH of <2.5 is necessary for the production of this syndrome.

The actual incidence of pulmonary acid aspiration in the surgical patient is unknown as it may occur as a subclinical problem manifesting itself as postoperative pneumonia, atelectasis or intraoperative or postoperative pulmonary dysfunction of unknown etiology. It is known, however, that certain anesthetics may increase the risk of this problem by increasing gastric acid production while others decrease this risk by doing the opposite. There is also evidence that premedication, especially heavy premedication, may reduce the risk of acid aspiration by decreasing acid production.

Other factors that increase the risk of pulmonary acid inspiration include patients who for whatever reason have a large volume of gastric fluid, patients with hiatus hernia with reflux, the presence of passive

regurgitation, patient positions that promote reflux or regurgitation, and failure to fast preoperatively.

In recent years attempts have been made, especially in the pregnant patient about to undergo anesthesia (a patient population most especially at risk of sustaining acid pulmonary aspiration because of delayed gastric emptying) to reduce both gastric volume and pH. The first drug group studied were the anticholinergic drugs (atropine, scopolamine). While these drugs can reduce gastric juice volume, their effects are quite variable. In addition, they have little influence on gastric pH and decrease gastric emptying and esophageal tone, both of which increase the risk of gastric reflux. Another undesirable effect of the anticholinergics is that heart rate is increased.

A second drug studied recently is glycopyrrolate. This compound reduces gastric volume and increases pH but it, like the anticholinergics, is not fool-proof. A recent study comparing glycopyrrolate, atropine, and patients receiving no drug (control) demonstrated that neither drug significantly altered the mean pH or volume of gastric juice in preoperative patients nor reduced the incidence of patients with gastric juice pH below 2.5.

Antacids have also been used to neutralize acid gastric juice contents in patients about to undergo operation but while they do increase pH they also increase gastric volume and thus increase the risk of reflux. Antacids possess the additional disadvantages of causing pulmonary damage themselves (when aspirated) and requiring administration at least 30 minutes before induction of anesthesia for effectiveness.

A couple of recently performed studies have indicated that while acid injection into the lung produces dramatic increases in pulmonary hemorrhage, exudates and edema and alkaline solutions produce no histologic changes (although they do increase pulmonary shunting) antacids produce bronchopneumonia. Thus, seemingly innocuous drugs may not be innocuous at all when aspirated into the lungs.

For many years you have heard how gastric acid is increased with histamine, gastric acid and acetylcholine. You've also heard about H_2 receptors and how histamine stimulates these receptors and Cimetidine blocks them. This all suggests that Cimetidine may be effective in acid pulmonary aspiration by decreasing acid production and gastric volume and thus decreasing the incidence and magnitude of pulmonary damage, should

aspiration occur.

Initial studies done with oral Cimetidine (400 mg) administered with preoperative premedicants indicated that the percent of patients with gastric pH above 2.5 was markedly increased over controls for up to 6-8 hours. Unfortunately, gastric volume was not significantly altered with this therapy. Another study demonstrated that oral Cimetidine only given immediately before operation is ineffective in increasing pH and reducing gastric volume. However, oral Cimetidine given the night before and immediately before operation does increase gastric pH. In the latter study the best regimen was either intramuscular or intravenous Cimetidine which both reduced gastric volume as well as increased gastric pH. Of the latter, IV therapy was best as it acted sooner and produced the most dramatic results. However, giving IV Cimetidine as routine preoperative medication is cumbersome in most hopsitals and as a result therapy employing Cimetidine orally at the hour of sleep the night before operation and IM just before operation seems equally effective. One study has demonstrated that this therapy is better than no Cimetidine, oral Cimetidine the morning of surgery or oral Cimetidine the night before and morning of operation.

Intravenous Cimetidine is gaining popularity in open heart surgery and in intensive care units to reduce G.I. bleeding secondary to gastric acid production. Preliminary findings (de Lange, S., unpublished data) indicate the compound has little effect on cardiovascular dynamics when given intravenously either before or during operation.

The infrequently occurring adverse effects of Cimetidine which have only been reported in a few patients receiving chronic, higher dose Cimetidine have not been found when the drug is given either before or during anesthesia (Stanley TH, unpublished data).

Thus, Cimetidine is a good compound to use in the pre or intraoperative period to reduce gastric volume and increase pH and should reduce the incidence and magnitude of acid pulmonary aspiration. It appears that IV is better than IM usage but that a combination of oral Cimetidine at the hour of sleep and IM preoperatively about one hour before operation will work fine in almost everyone.

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GENERAL PHARMACOKINETIC PRINCIPLES OF INDUCTION AGENTS

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INTRODUCTION

Drugs produce their pharmacological effect in biological systems by reacting with receptor sites, which are located in the target tissues. The intensity of effect of reversibly acting drugs depends on the degree of receptor occupation, which, in turn, is determined by the concentration of the drug in the direct environment of the receptors (biophase) and the affinity of the drug for the receptors. Usually, it is not possible to determine drug concentrations at the receptor sites in man, since these are not accessible for sampling. However, all tissues are supplied with plasma and it is obvious that a certain relationship must exist between drug concentration in plasma and the concentration in the biophase, although such a relationship may be complex. The plasma is easily accessible for sampling. Following the administration of a drug to man or animal, several processes take place: 1. absorption from the site of application to the plasma; 2. distribution from the plasma into organs and tissues, and 3. elimination by biotransformation (e.g. in the liver) or by excretion (e.g. through the kidney). As a consequence of these events, which partly occur simultaneously, the drug concentration in plasma changes with time. Likewise, the concentration in the biophase also changes and so does the pharmacological effect. In other words, changes in the time course of drug concentrations in plasma will affect the time course of drug action. It is for this reason that information on the kinetics of a drug in the body is of great interest for clinical practice in general and for anaesthesiology in particular. In anaesthesiology many drugs are being applied and their onset and duration of

action is one of the key features during operation. Pharmacokinetic data will help to optimize drug application, with respect to the choice of the appropriate drug and drug preparation, as well as with respect to a proper dosage regimen.

PHARMACOKINETICS AND PHARMACOKINETIC MODELS

Pharmacokinetics deals with the kinetics of absorption, distribution, metabolism and excretion of drugs and other substances in man or animals. Its purpose is to study the time course of drug concentrations in plasma and other fluids, tissues and excreta and to construct models suitable to interpret such data. The relationship between pharmacological response and concentrations of drugs or their metabolites in body fluids is also pertinent to pharmacokinetics. Several textbooks and reviews have recently been published in the area of pharmacokinetics and clinical pharmacokinetics (1 - 4).

One of the basic tools of science is the use of models to simulate and simplify real systems. In physiology and pharmacokinetics compartment models are often used to describe the behaviour of endogenous substances or exogenous substances, including drugs, although recently also more physiological models are being applied (1). Compartmental models assume that the biological system can be described as one or more connected pools, in which an amount of drug may be homogeneously distributed throughout an apparent volume of distribution. The transfer of drug between compartments is usually assumed to proceed by an apparent first-order process. In Fig. 1 a representation is given of the processes taking place after administration of a drug to the body. These involve consecutive and simultaneous competing rate processes or clearance processes, where clearance may be thought of as that volume of the total volume of a certain compartment which is totally cleared of drug per unit of time. Compartment O may for instance, represent the g.i. tract after oral administration of a drug and to the central compartment belong the plasma, blood cells, and the well-perfused organs and tissues. Additionally it may be distinguished between a peripheral compartment and a brain compartment which, for i.v. induction agents, includes the

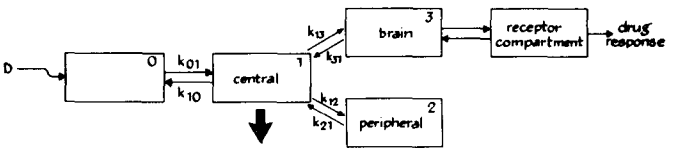

FIGURE 1. In this theoretical schema a representation is given of the various rate processes taking place in the body after administration of a drug. The k-symbols represent the rate or clearance constants to and from the various compartments. The heavy arrow from the central compartment indicates the elimination process of the drug from the body, either by excretion or by biotransformation or by a combination of both.

the receptors. The heavy arrow from the central compartment represents the elimination process of the drug from the body via the kidney (water soluble or hydrophilic compounds like induction agents) or via the lungs (volatile agents like many general anaesthetic drugs). This model on paper looks rather complex and although it may even be realistic, it should be realized that in practice the possibility of determining drug concentrations will generally be limited to the central or plasma compartment. In other words we generally are only able, at least in humans, to measure plasma concentrations and from these it is often rather difficult or impossible to extrapolate to the absolute concentration in certain discrete areas of the body. With regard to the concentration time-course in the various parts of the body it may, however, be somewhat simpler, if one assumes that after a certain time a distribution equilibrium is established between the various compartments, so that the concentration decay in every compartment ultimately parallels the

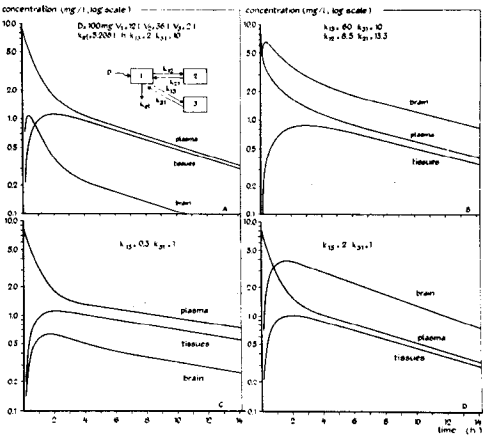

FIGURE 2. Theoretical curves representing drug concentration in plasma and tissues rapidly equilibrating with plasma (compartment 1), the other tissues of the body (compartment 2) and the brain (compartment 3). The pharmacokinetic parameters underlying these curves are given in A. and B. The clearance constants governing drug entry into the brain (k_{13}) and from the brain (k_{31}) are varied and the influence on the brain concentration and on the concentrations in the other two compartments is shown. The brain concentration may vary considerably despite comparable plasma concentrations.

the decay in plasma. Examples of such situations are given in Fig. 2, following rapid i.v. administration of drugs (directly into compartment 1) with different distribution characteristics. Compartment 2 represents a peripheral one and compartment 3 the brain. The values for the rate of brain penetration have been varied and it can be seen that only if brain penetration is rapid, immediately after drug administration high brain concentrations are achieved, which further closely follow the concentration