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## Review Article

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# Anaesthetic premedication: aims, assessment and methods

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### Contents

- Introduction
- History
- Aims of premedication
- Assessment of the results of premedication
- The preoperative visit
- Assessment of clinical drug trials
- Specific agents
  - Opiates
  - Anticholinergics
  - Benzodiazepines
- Special circumstances
  - Children
  - Cardiac patients
  - Other
- Conclusions

Anaesthetists have the opportunity to influence the course of their patients' anaesthetic with a preoperative visit and preoperative medication. A recent review documented pharmacokinetic data and side effects of drugs used for anaesthetic premedication.<sup>1</sup> In this article current aims of anaesthetic premedication are considered in the light of earlier ideas and the normal psychological reaction to anaesthesia and surgery. Methods of assessment of premedication are critically evaluated and the potential of the preoperative visit is examined. Efficacy of the three main drug groups used as premedicants is compared with special reference to newer agents. Finally some special circumstances, including premedication for children and cardiac patients, are considered.

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### History

The term "premedication" was first used in the United States of America and then in Britain during the 1920's. However, the technique of premedication was well established for some 40 or 50 years before. In the late 19th and early 20th century, atropine was used before chloroform anaesthesia to prevent "vagal inhibition," erroneously thought to be the cause of death during induction with chloroform. Morphine had also been used sporadically to reduce the amount of chloroform required.<sup>2</sup>

In the early 20th century, after ether replaced chloroform as the predominant anaesthetic agent, preanaesthetic medication with an anticholinergic agent and an opiate rapidly gained general acceptance. The anticholinergic reduced secretions and the opiate was thought to reduce reflex irritability and metabolic rate, rendering the patient "more susceptible to anaesthesia."<sup>3</sup>

Basal narcosis, the practice of rendering the patient unconscious before transfer to the operating room, using drugs such as paraldehyde or a barbiturate, became popular in the 1930's. The technique reduced induction trauma and postoperative vomiting by minimising the amount of ether used. However, the prolonged recovery was very demanding on nursing staff.

The introduction of thiopentone, tubocurarine and halothane in the 1940's and 1950's made smooth induction, light anaesthesia and rapid recovery possible. As side effects of anaesthesia were reduced, those of routine premedication with morphine and atropine or papaveretum and scopolamine were noticed. To minimise these premedication side effects, new drugs were developed. In the thirty years since the introduction of the first benzodiazepine, modification of the original molecule has produced a completely new group of drugs with potential as premedicants. Many clinical trials have been undertaken using these drugs and it seems an appropriate time to reassess the aims and methods of premedication.

### Aims of premedication

Many pharmacological and physiological reasons have been given for premedication. In 1955 Beecher wrote:

"It is fair to say that it has two general purposes: (a) to present an acquiescent, well-rested, serene patient to the surgeon and (b) to minimize insofar as possible the hazards of anesthesia and surgery."<sup>4</sup> As the cardiovascular and respiratory complications of anaesthesia have been reduced, psychological preparation of the patient has gained relative importance. Thus today, the main aim of premedication is to relieve fear and anxiety.

Unfortunately, there have been relatively few studies on the incidence and aetiology of preoperative anxiety. In 1964 Inglis<sup>5</sup> suggested that patients' fears and anxieties had changed over the preceding 20 years and that they were less worried about anaesthesia and surgery and more concerned about emotional and financial problems arising from hospitalisation. He also suggested that these anxieties began long before the anaesthetist's preoperative visit or medication. However, he did not present any data to support these beliefs. This lack of data was highlighted in an editorial two years later,<sup>6</sup> which also emphasised the difficulties involved in recognizing and measuring anxiety.

Norris, in an analysis of 500 patients on the day before operation, did provide some evidence that anaesthesia was a worry for relatively few (seven per cent).<sup>7</sup> Overall, although 60 per cent of the patients were anxious, one third of these could not express a precise reason for their anxiety. The most commonly specified cause of anxiety was the operation, followed by general health and leaving the family. Evidence to support Inglis' suggestion<sup>5</sup> that anxiety begins early has been produced by a psychiatrist using a psychological questionnaire.<sup>8</sup> She found raised anxiety scores before admission which continued to be elevated up to several days after surgery. In only a minority of patients did anxiety scores peak on the day of surgery. This finding obviously has widespread implications for patient management and gives us a rare insight into the natural history of anxiety in the surgical patient.

Other data on the incidence of anxiety come from the placebo and control groups in studies of premedication in which anxiety has been measured. The incidence of anxiety found by different authors varies from 11 to 80 per cent.<sup>9,10</sup> Part of this variation represents real differences in patient population and part is due to differences in methods of assessment. The higher figure comes from an early publication<sup>10</sup> which employed psychiatrists and a full psychological questionnaire, whereas the lower figure comes from a recent paper<sup>9</sup> which used the clinical impression of an investigator without psychiatric training. Thus, the more deeply one enquires, the more likely one is to find anxiety.

#### Assessment of the results of premedication

There are no accepted criteria defining a well-premedi-

cated patient, and authors have put varying emphasis on sleep, sedation, anxiolysis and drying of secretions. As a result, many different assessment protocols have been used. These usually involve measurement of a variety of psychological and physiological indices.<sup>11-13</sup> Arbitrary scales are used, depending on how desirable each measurement is thought to be by a particular author. The weighting given to any one variable, and the total score considered to be satisfactory, also varies from group to group.<sup>14</sup>

A baseline for both psychological and physiological variables is essential, so that treatment groups can be compared. In the case of anxiety, anxiolytics have been shown to have more effect on anxious rather than on nonanxious patients.<sup>15</sup> It is thus very important to demonstrate that all groups have a similar level of anxiety before treatment.<sup>16</sup> Pretreatment anxiety levels may affect the interpretation of the results.<sup>17,18</sup> Very often a baseline is not measured,<sup>17,19</sup> or only the change in the level of anxiety is given.<sup>20</sup>

Despite the growing awareness of the importance of anxiolysis in premedication, anxiety is difficult to quantify and some authors have omitted its assessment altogether.<sup>21,22</sup> Although many techniques have been employed to measure anxiety, they can be subdivided into four groups: observer's impression, physiological variables, hormonal measurements and patient self-assessment.

Anxiety is a subjective phenomenon; the term includes feelings of apprehension, uncertainty and fear, which all of us mask to a variable degree. Sedation allays excitement and renders the patient calm. It is difficult to categorise the majority of patients who are neither extremely anxious nor absolutely calm. There is also a temptation to equate drowsiness with anxiolysis or sedation<sup>23</sup> although they have been shown not to be synonymous:<sup>24,25</sup> drowsiness can coexist with anxiety or excitement. Studies should use as few observers as possible. If more than one is used, the results should be compared.<sup>11</sup>

The measurement of physiological variables, as an indirect assessment of sympathoadrenal activity, has been usefully employed to determine anxiety. Pulse rate and blood pressure have been used most commonly and caused Nisbet and Norris<sup>12</sup> to recategorise 25 per cent of patients graded by observer's impression alone. Respiratory rate and end-tidal CO<sub>2</sub> have been measured to assess anxiety-induced hyperventilation. Electrical resistance or blood flow to the skin have been measured as have muscle tone, eye movements and pupil size. The measurements themselves must not cause anxiety and the apparatus must be portable. Several measurements should be made to acquire a true resting level and then the response can be measured to a stimulus such as an intravenous injection. Individuals demonstrate a range of responses to the

same stimulus. Thus a reaction is more likely to be detected if several physiological measurements are made. This may take more time than is available in a study of premedication.<sup>26</sup>

In one study antidiuretic hormone concentrations were significantly lower in patients premedicated with a benzodiazepine compared with results from patients receiving placebo. The former patients also had a higher overall score for premedication; however, there was no significant correlation between antidiuretic hormone concentration and observer assessment of sedation, apprehension or excitement.<sup>27</sup> Comparisons of antidiuretic hormone concentrations and patient self-assessment of anxiety have not been done. However, plasma catecholamines have been measured and significant correlation found between the mean percentage change in visual analogue score for anxiety and the mean percentage change in epinephrine concentration.<sup>28</sup>

Having the subjects rate their own anxiety can be done in one of three ways. The simplest method is a form of verbal scale. This has certain limitations, in that the categories are not necessarily equal and will mean different things to different people. There is a tendency for patients to use the central categories alone, with subsequent loss of resolution and the scores are only amenable to limited statistical analysis. The second form of assessment consists of a psychological questionnaire. These are usually complex, time consuming and require patient cooperation and a degree of verbal sophistication. They are not repeatable at frequent intervals and were designed and validated on psychiatric patients. The third method of assessment is the visual analogue scale (VAS), which has been used to measure mood and pain, in both psychiatric and normal subjects.<sup>29,30</sup>

The VAS has several advantages; it is easy to understand and quick to complete; the patient and assessor are not restricted to a few graded terms and it also appears to eliminate the preference for the midzone seen with the verbal rating scales.<sup>30</sup>

Studies including both observer and patient assessments of anxiety have sometimes shown interesting inconsistencies. In the majority of cases an observer detected a significant decrease in anxiety after premedication in contrast to the patients' self-assessment of no change.<sup>20,31-33</sup> The most probable explanation for this is the confusion between drowsiness and anxiolysis. However, in more than one study of benzodiazepines, the VAS has demonstrated significant anxiolysis<sup>34</sup> or the verbal score has demonstrated significant variation with time,<sup>35</sup> when the observer has not. Retrospective assessment by patients may underestimate the true incidence of anxiety due to amnesia.<sup>33,36,37</sup>

In conclusion, it is important to measure the patients'

subjective reaction to premedication in addition to observer evaluation. Plasma epinephrine concentration may provide an objective measurement of anxiety but requires further evaluation. A standardised protocol for assessment of anaesthetic premedication would facilitate comparison of studies from different institutions.

### The preoperative visit

In view of the range and diversity of fears expressed by patients, it would seem unlikely that a routine preoperative visit could significantly reduce anxiety. However, Egbert<sup>24</sup> demonstrated that a visit by an anaesthetist was superior to barbiturate premedication in reducing anxiety as assessed by both observer and patient. This study has been followed by others documenting the psychological impact of a preoperative visit. However, the impact is not always beneficial. Williams<sup>38</sup> demonstrated the differing effects of two types of preoperative interview on patients. Highly anxious patients had their anxiety reduced by both the cursory and the supportive interview, whereas relatively non-anxious patients had their anxiety increased by the cursory interview.

A preoperative visit may reduce anxiety in several ways.<sup>40</sup> Firstly, information given may help to relieve uncertainties or misconceptions. In support of this theory Leigh<sup>40</sup> demonstrated the beneficial effect of a booklet about anaesthesia which the patient read on the day of surgery. Secondly, the visit gives the patient an opportunity to discuss any fears and to be reassured. Supportive interviews seem to be superior to information alone.<sup>38,40</sup> Finally, some patients probably benefit if given the opportunity for self-help or coping. They can be taught how to relieve anxiety with relaxation and breathing exercises and be made aware that sedatives and anxiolytics are available on request.

The net effect of a preoperative interview will depend on the content, format, timing, personality of the interviewer and the personality and circumstances of the patients. Studies which hope to elucidate the anxiolytic effect of the preoperative visit must standardise all the variables other than those under study. Placebo groups are essential to differentiate psychological from pharmacological effects.

### Assessment of clinical drug trials

Differences between drugs are more likely to be demonstrated if the patient population is homogeneous and large. Comparisons of groups of 100 patients has been shown to give reasonably reproducible results for opiate premedication.<sup>41</sup> Larger numbers may be required to give consistent results from non-soporific drugs. Furthermore, drug administration should be randomised and double-blind. When these precautions are not taken,<sup>42</sup>

bias can influence observations, especially if they are subjective.

There has been some criticism of placebo and controlled trials;<sup>17</sup> however, both are important in the study of premedication, because only with their use can drug effect be differentiated from the effect of the preoperative visit<sup>41</sup> and placebo.<sup>34</sup> There should be no ethical problem with such a trial, since no premedication is universally accepted as being beneficial and placebo has been rated as very satisfactory for ease of induction in as high as 87 per cent of patients.<sup>31</sup> The inability to demonstrate any difference between two treatments or doses,<sup>44-47</sup> in the absence of placebo, is very difficult to interpret. It may imply equivalence, but equally it may be that the method is too insensitive to differentiate between treatments which do differ considerably from each other. Control groups must come from the same patient population; for example, it is probably invalid to compare inpatients with day surgery patients.<sup>48</sup>

Having established a difference between drug and placebo it would be even more persuasive if a dose-response relationship could be demonstrated.<sup>31</sup> However, this is difficult, because the methods of assessment of anxiolysis are not sensitive and the best anxiolytics, the benzodiazepines, have a very variable effect on different individuals.

It may be acceptable to omit repetition of a treatment group if an investigator has demonstrated the reproducibility of his results in previous studies.<sup>26,41</sup> However, omission is not justifiable on the basis of one previous study;<sup>49</sup> over time one author, using one method of assessment, can modify his opinion of the subjective effect of an active treatment.<sup>14,50</sup> For example, Dundee<sup>41</sup> has demonstrated highly variable incidence of both subjective and objective effects of atropine and placebo recorded in one unit over a six-year period.

In looking for side effects of premedication, assessment must continue beyond the preoperative period and therefore the anaesthetic and surgery must be the same for all patients. Pre- and postoperative care can be standardised by using one unit or ward. The side effects sought will depend on the drugs under investigation and the number found will depend in part on the extent of the search. Dundee<sup>41</sup> found emetic sequelae more consistent when studied for six hours rather than for one hour. Nursing records will give an underestimate of emetic sequelae.<sup>18</sup> Studies which purport to demonstrate an absence of "hangover" or return to "street-fitness" must carry out an appropriate selection of psychomotor tests.<sup>51</sup> It is unacceptable to claim the absence of side effects which have not been specifically sought.<sup>52</sup> It is equally fruitless to demonstrate an absence of side effects but not to attempt to demonstrate any benefit.<sup>53</sup>

In summary, drug trials of anaesthetic premedication should be randomised and double-blind with placebo groups. Study protocols should be standardised for as long as drug effects are sought.

### Specific agents

#### *Opiates*

These drugs were the first soporifics and analgesics available and their continued use has, in part, been due to tradition.<sup>4</sup> Opiates have been described as aiding a smooth induction, depressing the cough reflex and reducing the amount of volatile agent required.<sup>34</sup> However, the clinical significance of these effects can be questioned with modern intravenous induction agents and potent, non-irritant volatile agents. The claim that opiates induce a state of euphoria is also unjustified. Morphine produces dysphoria in 80 per cent of normal subjects and euphoria in only ten per cent.<sup>55</sup> Using a psychological questionnaire, Wassenaar<sup>56</sup> showed that papaveretum (pantopon) did not significantly reduce anxiety, but it did significantly increase psychological depression. A new preparation of oral controlled-release morphine has also been shown not to significantly decrease anxiety although it was soporific.<sup>57</sup> Investigators who considered opiates satisfactory have emphasised sleep rather than anxiolysis and have not looked for postoperative side effects.<sup>12</sup> Dundee,<sup>58</sup> studying a variety of premedicants, scored papaveretum with hyoscine highly for efficacy with average toxicity and postoperative emetic sequelae. However, in comparison, diazepam scored well for efficacy with minimal side effects. Opiates cause detectable respiratory depression in therapeutic doses in fit volunteers.<sup>59</sup> This may be clinically significant in certain patients with impaired respiratory reserve. Other potential problems include: postural hypotension, constriction of the bronchi and sphincter of Oddi, delayed gastric emptying, constipation and urinary retention.

Recent advances in opiate therapy include the development of potent, short-acting agonists for intraoperative use and partial agonists.<sup>60</sup> The latter have some interesting characteristics, including a ceiling for both therapeutic and toxic effects. The therapeutic ceiling leads to some difficulty in interpreting relative potencies since these will depend on the strength of the stimulus.<sup>61</sup> In general, the partial agonists have relatively low abuse potential. They produce varying degrees of undesirable psychotomimetic effects<sup>62</sup> and are unlikely to reduce preoperative anxiety.<sup>63,64</sup> The combined use of partial agonists with pure agonists will produce a variable degree of antagonism.

Thus, as a result of the multiple side effects and lack of demonstrable advantages, there seems to be no jus-

tification for the use of old or new opiates for premedication unless the patient is in pain or is to be subjected to painful procedures before induction of anaesthesia.

#### *Anticholinergics*

The use of these drugs in premedication has a long history, since the late 1860's. Although declining in popularity, anticholinergic premedication was still practised by 75 per cent of anaesthetists surveyed during the 1970's.<sup>65</sup>

Beneficial effects attributed to these drugs include drying of secretions, most completely achieved by administration in the preoperative period. Some investigators have found excessive salivation a problem in the absence of anticholinergic premedication,<sup>66,67</sup> especially during ENT operations, and despite the use of intravenous atropine at induction of anaesthesia. However, the value of routine anticholinergic premedication has been questioned by many authors,<sup>68-74</sup> who have not found secretions a problem. In the absence of anticholinergic premedication, patients certainly have more secretions but they are easier to remove since they are less tenacious.<sup>72</sup> No increase in complications has been documented; on the contrary, the incidence of sore throats and chest complications may be reduced<sup>68</sup> and patients complain less of dry mouth.<sup>70,73</sup>

Any reduction attributable to anticholinergics in the incidence of laryngospasm is probably due to reduced secretions.<sup>75</sup> However, one large retrospective survey of computerised records<sup>76</sup> actually demonstrated a significant increase in the incidence of laryngospasm when anticholinergics were used.

The suppression of cardiovascular vagal reflexes is another indication for anticholinergic premedication. However, the predominant response to laryngoscopy, tracheal intubation and surgery is sympathetic<sup>77</sup> and anticholinergic premedication will only accentuate this, leading to a higher incidence of tachycardia.<sup>73,74,78</sup> A significant increase in the incidence of dysrhythmia has been reported after atropine or hyoscine premedication but not after glycopyrrolate.<sup>71,79,80</sup> One study also demonstrated a significantly greater increase in blood pressure with atropine or glycopyrrolate premedication compared with placebo.<sup>81</sup>

After intramuscular anticholinergic premedication there is still approximately a 50 per cent incidence of bradycardia secondary to repeated doses of suxamethonium or the oculocardiac reflex.<sup>82-84</sup> In contrast, intravenous anticholinergics in appropriate dosage protect against these reflexes in all but 10-20 per cent of patients.<sup>84,85</sup> However, intravenous anticholinergics produce approximately a 25 per cent incidence of dysrhythmia, although most are supraventricular and not clinically significant.<sup>86,87</sup>

Subsidiary benefits which have been claimed for anti-

cholinergic premedication include the antiemetic action of atropine and hyoscine and the soporific action of hyoscine.<sup>88</sup> These effects can be achieved with fewer side effects by more specific drug therapy. Glycopyrrolate and atropine may reduce gastric juice acidity and volume,<sup>89,90</sup> but this is offset by the reduction in lower oesophageal barrier pressure<sup>91</sup> and decreased gastric emptying.<sup>92</sup>

The ocular effects of anticholinergics include pupillary dilation and loss of accommodation. Hyoscine has the most potent ocular effects and can cause prolonged blurred vision postoperatively. Atropine and glycopyrrolate given intramuscularly in normal premedicant doses have no effect on pupillary size or intraocular pressure in healthy volunteers.<sup>93</sup> Normal premedicant doses of hyoscine and relatively larger doses of atropine intramuscularly have been shown to cause significant pupillary dilation.<sup>94</sup> However, a study of glaucomatous patients failed to demonstrate any significant pupillary dilation or increase in intraocular pressure after similar doses of atropine or hyoscine.<sup>95</sup> The detrimental effects of hyoscine and atropine on memory may cause problems for day-surgery patients.<sup>96-98</sup>

There seems little justification for the routine use of anticholinergic premedication. If a dry mouth is required for oral surgery or fibreoptic intubation of the trachea, glycopyrrolate is the agent of choice, having fewer side effects than atropine or hyoscine.<sup>71,79</sup> However, its potency, long duration of action<sup>98</sup> and patient discomfort from dry mouth must be weighed against any possible benefit from its use.

#### *Benzodiazepines*

Since the synthesis of the first benzodiazepine, chlordiazepoxide, in the late 1950's,<sup>100</sup> many related compounds have been developed and marketed. A number of these have been shown to be capable of reducing anxiety preoperatively, including: diazepam,<sup>19,20,32</sup> lorazepam,<sup>33,101</sup> flunitrazepam,<sup>101,102</sup> temezepam,<sup>16,32</sup> oxazepam<sup>103</sup> and midazolam.<sup>25,104,105</sup>

However, some studies have been unable to demonstrate anxiolysis by these drugs. Low initial anxiety and the placebo effect may have masked drug effect.<sup>34,106</sup> In other studies the drug was given by an inappropriate route or assessed too soon after administration.<sup>31,34,103</sup> Insensitive methods of assessment of anxiety were used by some investigators.<sup>100,107</sup> However, in studies of triazolam 0.25 mg<sup>20</sup> and lorazepam 2.5-5 mg,<sup>33</sup> visual analogue scores failed to demonstrate any patient anxiolysis, although both treatment groups were sedated and had observer assessed decreases in anxiety. Thus there is a problem when comparing studies, since less than 50 per cent of recent reports have assessed subject-rated anxiety as well as an observer's impression.

Most benzodiazepines have a sedating and soporific as well as an anxiolytic action. One exception is tofizepam which does not seem to have any anxiolytic action until at least two doses have been given and even then it is not sedating or soporific.<sup>108,109</sup> Amnesia is another action of benzodiazepines thought to be advantageous. However, there is some evidence that only a minority of patients would choose amnesic premedication.<sup>110</sup>

The action of benzodiazepines on memory affects both the registration and consolidation of information.<sup>111</sup> The amnesia is dose-related, and parallels the increase in sedation, and is found with oral and parenteral administration. Lorazepam has a delayed but prolonged effect when given orally or parenterally. Four mg orally produced nearly 80 per cent amnesia for recall of cards, with a maximum effect from 90 to 240 minutes after administration.<sup>112</sup> In comparison, diazepam 20 mg and flunitrazepam 1 mg orally produced 30–65 per cent amnesia for cards at 60 minutes. Onset of the latter drugs is faster and duration much shorter than lorazepam regardless of the route of administration, but especially noticeable with intravenous administration.<sup>113</sup>

Amnesia, for experimental stimuli such as cards, is usually greater than amnesia for more emotionally significant events. Although some studies have shown 70 per cent amnesia for an intravenous injection after lorazepam administration<sup>33,113</sup> others have demonstrated only 23–43 per cent amnesia for perioperative events.<sup>114</sup> All patients could recall their intravenous injection after 20 mg of diazepam orally.<sup>113</sup> Midazolam 70  $\mu\text{g}\cdot\text{kg}^{-1}$  intramuscularly produced amnesia for an intravenous injection in nearly 50 per cent of patients.<sup>105</sup> All the studies of intravenous administration have demonstrated greater amnesia with midazolam than an equivalent dose of diazepam.<sup>44,115,116</sup> The extent and duration of amnesia after oral midazolam has yet to be established.

Retrospective amnesia is an uncommon event with all these drugs, and no drug by any route gives anterograde amnesia to all patients. Thus every patient should be treated as though aware and expected to have recall of perioperative events.

One feature of benzodiazepine premedication which is appreciated by both patients and nursing staff is oral administration. This does not lead to an increased risk of aspiration when compared with intramuscular opiate premedication.<sup>117</sup> One study demonstrated a significant decrease in gastric volume and acidity with oral compared to intramuscular administration of diazepam.<sup>118</sup> Newer formulations employing sublingual or buccal absorption have been developed for some benzodiazepines (flunitrazepam,<sup>35</sup> oxazepam,<sup>52</sup> lorazepam<sup>119</sup> and temezepam<sup>120</sup>) and may be useful for patients unable or unwilling to swallow tablets.

Diazepam is better absorbed after oral administration, the same dose giving earlier and higher peak plasma concentrations than after intramuscular administration.<sup>121,122</sup> Absorption of diazepam is poor after intramuscular injection, even with the newer fat emulsion preparation (Diazemuls), although this does have the advantage of being less painful.<sup>123</sup> Intramuscular injections of diazepam in propylene glycol are significantly more painful than placebo regardless of site or needle length.<sup>124,125</sup> The clinical effect is also greater after oral than after intramuscular administration.<sup>118,124</sup> Yet, despite the evidence of poor efficacy and pain on injection, papers still appear comparing intramuscular diazepam with other premedicants.<sup>126</sup>

In comparison with other premedicant drugs, benzodiazepines have relatively few side effects. There is little evidence that benzodiazepines given orally cause significant respiratory depression. One study demonstrated some respiratory depression one and two hours after diazepam 5 mg given orally<sup>127</sup> and another demonstrated a significant drop in  $\text{PaO}_2$  one hour after 10 mg.<sup>128</sup> Neither of these changes was found after 10 or 20 mg of diazepam in a third study.<sup>42</sup> Noninvasive studies using a pneumotachygraph demonstrated a reduction in tidal volume, minute volume and the abdominal contribution to breathing after oral flunitrazepam and intravenous midazolam.<sup>129,130</sup> This is a new technique of study which needs further validation before the significance of these changes can be assessed. Certainly intravenous benzodiazepines cause central respiratory depression as evidenced by a decrease in the mouth occlusion pressure and a flattening of the  $\text{CO}_2$  response curve.<sup>131,132</sup> Intramuscular opiates cause much more profound depression and actually shift the  $\text{CO}_2$  response curve.<sup>59</sup>

Another side effect of opiates which benzodiazepine lack is an emetic action.<sup>58</sup> Some authors have gone so far as to claim an antiemetic action for benzodiazepines.<sup>133–135</sup> However, in most studies emesis in the benzodiazepine-treated group does not differ significantly from the placebo group. Some authors have reported a decreased incidence in the occurrence of headache, frequent after anaesthesia, with diazepam premedication<sup>101,103</sup> but others have found the reverse.<sup>48</sup>

One major drawback of benzodiazepines is the variability of clinical effect. Diazepam,<sup>122,123,136</sup> lorazepam,<sup>137</sup> flunitrazepam,<sup>138</sup> nitrazepam<sup>48</sup> and midazolam<sup>123</sup> have all been shown to give very variable plasma concentrations after oral, rectal or intramuscular administration. Concurrent medication may affect absorption after oral administration. Atropine and opiates delay, while metoclopramide hastens, diazepam absorption<sup>139</sup> and antacids have been shown to produce both effects.<sup>140,141</sup> First pass metabolism may not diminish clinical effect if active

metabolites are formed.<sup>142</sup> Secondary peaks of diazepam and lorazepam have been measured at five to six hours after administration and are thought to be due to enterohepatic recirculation.<sup>137,143</sup>

The great variation in plasma concentrations becomes less of a concern when it is realised that only a minority of authors have found any correlation between total plasma concentration and clinical effect. Richardson<sup>135</sup> did find significantly higher plasma concentrations of flunitrazepam and diazepam in those children amnesic for induction of anaesthesia. More recently, Mattilla<sup>138</sup> found correlation between sedation and plasma flunitrazepam concentrations. Similarly, Kanto<sup>144</sup> found good correlation between sedation and plasma midazolam and the concentration of its active metabolites. Using the same combined serum concentrations, Crevoisier<sup>142</sup> found good correlation with tests of psychomotor function.

As a result of very high protein binding the concentration of free drug is independent of the total amount of drug present.<sup>143</sup> The significance of this is borne out by the finding that the induction time for intravenous midazolam is proportional to the plasma albumen concentration.<sup>145</sup> Plasma concentrations do not necessarily reflect concentrations in other compartments. The slow onset of action of lorazepam regardless of route is at least in part explained by its slow penetration of the CSF.<sup>146</sup> One author has suggested that it is the rate of rise of plasma concentration rather than the final concentration which determines clinical effect.<sup>147</sup> Furthermore, patient personality may have an effect on the rate of absorption,<sup>145</sup> and age certainly affects the pharmacokinetics of benzodiazepines.<sup>143,149,150</sup>

The older benzodiazepines all have a long duration of action which may be attributable to the parent compound and/or active metabolites. The resultant advantage is that timing of premedication is not critical. However, flunitrazepam<sup>102</sup> and nitrazepam<sup>151</sup> have detectable effects the day after administration and the plasma concentrations of lorazepam 24 hours after administration would suggest that CNS effects were still present.<sup>152</sup> This may be desirable for inpatients for whom the hangover from night sedation can contribute to premedication. Such a long duration of action would, of course, be detrimental for out-patients.

Derivatives with no active metabolites such as temezepam and oxazepam should have a shorter duration of action. Temezepam has some promise; two studies found performance to be unimpaired two and three to four hours postoperatively.<sup>16,103</sup> Recent studies have determined its elimination half-life to be 10–20 hours, longer than originally estimated.<sup>153</sup> It may have only marginal advantages over diazepam for occasional use.<sup>151</sup> Oxazepam is only slowly absorbed and there is delayed impair-

ment of performance.<sup>151</sup> Two studies could not demonstrate any anxiolysis with this drug, possibly because the patients were tested too soon after administration.<sup>34,103</sup> Another group of benzodiazepines including triazolam and midazolam are rapidly metabolised by oxidation. Triazolam failed to produce significantly more anxiolysis than placebo, and it impaired psychomotor performance at three hours postoperatively more than diazepam or placebo.<sup>20</sup> Midazolam probably has more potential. It is rapidly acting with maximum effect at 30 minutes and a short elimination half-life of one to two hours after oral administration. It has been shown to be anxiolytic, sedative and amnesic. Sjøvall<sup>102</sup> detected some residual effects the morning after its use as night sedation. We still await studies on psychomotor performance after the use of midazolam in day cases.

Although their effect is predictable statistically rather than for the individual, benzodiazepines still come nearer than any other drug group in best allaying anxiety without the production of side effects.

### Special circumstances

#### Children

Premedication for children is even more controversial than that for adults. Over the years fashions have changed for the amount of sedation and route of administration.<sup>3</sup> Requirements vary with age group<sup>154</sup> and 70–80 per cent of older children behave satisfactorily without sedative premedication.<sup>14,154,155</sup> Many preparatory techniques have been used to reduce fear and increase adjustment, including rehearsal and modelling using film.<sup>39</sup> Even very young children benefit from information in addition to supportive care.<sup>157</sup>

The merits of the various routes of administration of premedication have been debated. Intramuscular injections are disliked, and oral medication, even when palatable and of small volume, is often rejected. This has led to renewed interest in the rectal route<sup>158,159</sup> which seems to be well accepted by young children.<sup>160</sup> However, more information is required about absorption<sup>161–164</sup> and mucosal irritation.<sup>165,166</sup>

There is little evidence that either extreme of stormy or "steal" induction causes postoperative psychological disturbance.<sup>156,167</sup> In one study the presence of the child's mother at induction led to significantly better behaviour at induction and reduced separation anxiety postoperatively.<sup>168</sup> If other studies support this finding, then we need to know which age group benefits and whether there are circumstances in which parental presence is a disadvantage. Guidelines could be established and adjustments made in operating theatre routine to accommodate a parent at induction of anaesthesia when appropriate.

Given that many children will behave in the absence of premedication, it is important that any drug used is relatively free of side effects. Opiates have been shown to cause respiratory depression<sup>169-171</sup> and increase the incidence of postoperative vomiting.<sup>172,173</sup> A new non-narcotic analgesic, nefopam, was also found to increase the incidence of vomiting after anaesthesia.<sup>174</sup> High doses of trimeprazine can cause pallor and hypotension.<sup>175,176</sup> Droperidol can cause extrapyramidal reactions.<sup>177</sup> One group of drugs which has maintained its popularity for premedication in children is the anticholinergics. However, the only justification for their continued use preoperatively is to reduce salivation, and as in adults, glycopyrrolate is superior in this respect.<sup>178</sup> Intravenous atropine or glycopyrrolate at induction gives more complete protection from the bradycardia associated with succinylcholine and halothane<sup>179-181</sup> and avoids prolonged discomfort from a dry mouth.

Benzodiazepines have produced satisfactory demeanor in some studies.<sup>120,182,183</sup> These drugs need to be compared with placebo so that environmental conditions and personality effects are considered.<sup>168,184</sup> As with adult studies it is necessary to standardise the pre-, per- and post-operative management of the different treatment groups. In studies on children it is also important to subdivide the treatment groups according to age or to compare drug effects in one narrow age group.<sup>155</sup>

#### *Cardiac patients*

These patients offer a new challenge and means of assessment of premedication. In a prospective study, 18 per cent of patients for coronary artery bypass surgery arrived at the operating room with new ischaemic changes on their ECG.<sup>185</sup> The same study demonstrated new ischaemic changes to be associated with an increased risk of post-operative myocardial infarction and that the risk was independent of whether the ischaemia occurred pre- or peroperatively. Premedication varied in this study and not all patients were receiving beta-adrenergic blockers.

Two studies considered the related problem of haemodynamic changes and angina occurring during the insertion of intravascular cannulae and catheters for invasive monitoring. The patients received a combination of diazepam, morphine and hyoscine as premedication. In one study,<sup>186</sup> the patients also had topical nitroglycerine ointment and were continued on beta-adrenergic blockers. No patient suffered an episode of angina or a significant increase in pulse rate or systolic pressure. In the other study<sup>187</sup> patients on beta-adrenergic blockers suffered similar changes in rate-pressure product as those without beta-adrenergic blockade but 50 per cent of the latter had an episode of angina. Thus beta blockade does seem to offer some protection.

Intravenous administration of beta blockers significantly attenuates the increase in pulse rate but not the increase in systolic pressure at laryngoscopy,<sup>188-190</sup> whereas oral administration over a few days offers lower blood pressure before and during laryngoscopy.<sup>191</sup> The minimum duration of beta blockade for maximum protection has yet to be determined.

#### *Other special circumstances*

Recent reviews have discussed the preoperative management, including premedication, of patients with respiratory,<sup>192,193</sup> renal<sup>194</sup> and liver<sup>195</sup> disease. The pharmacokinetics and pharmacodynamics of benzodiazepines are altered in patients with cirrhosis of the liver. Even a shorter-acting drug, such as midazolam, is eliminated more slowly and its effect on psychomotor function prolonged, in comparison with patients without liver disease.<sup>196</sup> Midazolam may, however, offer some advantage over the longer-acting drugs, such as diazepam, for patients with cirrhosis.

Patients with a history of anaphylactic reactions require special investigation.<sup>197</sup> Pretreatment with anti-histamines, using both H<sub>1</sub> and H<sub>2</sub> receptor blocking agents (for example, a slow intravenous infusion of diphenhydramine 1 mg·kg<sup>-1</sup> and cimetidine 4 mg·kg<sup>-1</sup>) will attenuate a reaction.<sup>198</sup>

Alert and apprehensive neurosurgical patients probably benefit from premedication. Opiates cannot be recommended because ventilatory depression, vomiting and pupillary constriction are particularly undesirable in this group of patients. Prolonged drowsiness has been reported after lorazepam,<sup>199</sup> making it difficult to monitor the patient's neurological condition.

Premedication for the obstetric patient is usually restricted to measures designed to reduce the volume and acidity of stomach contents. Midazolam may prove to be a safe option for the particularly anxious parturient since placental transfer is low; however, ability of the neonate to metabolise midazolam is unknown.<sup>200</sup>

Day surgery patients do not usually receive premedication since there is little time for drugs to act and there is justifiable concern that premedication may delay recovery.<sup>201</sup> Moreover, there is some evidence that this group have a low level of anxiety<sup>202</sup> and it is difficult to demonstrate any benefit from premedication. However, anxious patients who are otherwise suitable for day care surgery could benefit from one of the newer, shorter acting benzodiazepines. Which, if any, of these drugs is superior in terms of anxiolysis and lack of postoperative effect is as yet unclear. There are no studies to date showing both a therapeutic effect and a lack of postoperative impairment of psychometric function after premedication in day surgery patients.<sup>53,203</sup>



### Conclusions

This article highlights our ignorance of the aetiology and natural history of preoperative anxiety, especially when considering particular patient subgroups. There is some evidence that we should give information and drug therapy much earlier than is currently practised; this will involve hospital personnel other than anaesthetists and perhaps even family physicians.

New tests are available to measure the efficacy of premedication but the validity of some of these has yet to be established. A protocol incorporating objective, subject rated and observer assessments of anxiety, which is acceptable, and gives reproducible results in different centres has yet to be devised.

There is little justification for the continued use of opiate premedication except for the treatment of pain or in preparation for painful procedures. A combination of opiate and benzodiazepine premedication does not adequately protect the cardiac patient for the insertion of invasive monitoring, in the absence of beta blockade. Anticholinergics should only be used for premedication when adequate blockage of salivation cannot be achieved predictably with intravenous administration at induction.

Benzodiazepines come nearest to the ideal of anxiolysis with minimal side effects. However, the role of the newer shorter acting drugs has yet to be established. The number of benzodiazepines currently available cannot be justified in terms of diversity of action, duration or side effects. Certainly an anaesthetist's requirements could be satisfied with two or three compounds of varying duration which could be administered by both parenteral and oral routes.

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