AN INTRODUCTION TO FBA.1420
A new Non-barbiturate Intravenous Anaesthetic

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SUMMARY
The action of a new intravenous non-barbiturate anaesthetic FBA.1420 (propanidid) has been studied in 550 patients. The period of narcotic action is short and recovery is rapid and uneventful. A brief hypotensive phase occurs during induction of anaesthesia. Coincident with the hypotension a period of hyperpnoea occurs which is usually followed by a period of respiratory depression. The respiratory depressant effect of suxamethonium was found to be enhanced by the presence of FBA.1420 but preliminary cat nerve-muscle and human electromyographic studies suggest that this interaction is not a neuromuscular phenomenon. Involuntary muscle movements were rarely marked. Laryngeal spasm did not occur but hiccough and coughing were occasional accompaniments of induction. The incidence of thrombophlebitis was low. Hepatotoxic and haematological investigations showed no significant abnormalities. The overall conclusion is that the eugenol derivative FBA.1420 is a safe short-acting intravenous anaesthetic.

FBA.1420 is a eugenol derivative, chemically not unlike G.29.505 but differing in having a propoxy-acetyl in place of the allyl group. Whereas G.29.505 is known to be inactivated by oxidation of its alkyl radicle, FBA.1420 appears to be decomposed by enzymatic splitting of its ester bond (J. Putter, personal communication, 1962). The breakdown products are inactive anaesthetically. Esterification is said to occur predominantly in the liver which appears capable of destroying half a systemic dose of 500 mg within 2–3 minutes and to a lesser extent by enzymes in plasma and kidney. It is possible that some breakdown of the molecule may take place by demethylation or splitting of the acid amide bond.

PHYSICAL PROPERTIES AND PRESENTATION
FBA.1420 is a yellowish-coloured oil with a boiling point of about 210°C. A 5 per cent preparation is made by the addition of a 20 per cent aqueous solution of polyoxyethylated castor oil (Cremphor El) which acts as a solubilizing agent and diluting vehicle. The preparation is clear, oily to the touch, bitter to the taste and smells faintly of castor oil. The present ampoule contains 10 ml of the 5 per cent preparation. It appears to have an extensive shelf life, at least eighteen months, and is ready-made for injecting. It possesses a viscosity such that a No. 1 gauge needle needs to be used with a 10 ml syringe in order to achieve injection at the rate of 1 ml/sec. The admixture of 20 per cent water, or any aqueous solution, appears to reduce the viscosity by a half, which can be regarded as convenient after the assessment of dosage on a dose/weight basis.

CLINICAL STUDY
The study was undertaken to gain a broad impression of the drug during normal clinical practice. For this purpose 500 unselected male and female patients, between the ages of 15 and 80 were given FBA.1420 as an anaesthetic induction agent following various premedicants. Fifty unselected out-patients within the same age group were given the agent as the sole anaesthe-
tic without premedication. The patients in the first half of each group were given the drug in the dose of 5 mg/kg and those in the second half 10 mg/kg. With both dosages an injection speed of 50 mg/sec was used. In patients who were not considered to be in first-class health, and in patients over the age of 60 the dosages were scaled down appropriately. Anaesthesia was attempted in ten patients given the drug by intravenous transfusion as the sole general anaesthetic, five in conjunction with epidural analgesia, and five lower abdominal operations were attempted without any additional analgesia or anaesthesia except for sedative premedication. Electrocardiographic monitoring was undertaken during anaesthesia in twenty-five patients. Subsequently haematological investigations and liver function tests were carried out.

Nervous system.

The drug gives a pleasant anaesthetic induction with no pain at the site of injection. Consciousness is lost after one arm-brain circulation time and the pupils often become widely dilated. Three patients given 5 mg/kg doses were considered inadequately narcotized. The pupillary, corneal, and laryngeal reflexes usually remain active, but a finger can be introduced to the pharynx without eliciting reflex. Masseteric relaxation is only pronounced with the higher dosage and will permit laryngoscopy and endotracheal intubation—although this will usually be associated with reflex activity. Muscle tone is generally diminished and involuntary muscle movements are rarely seen. In the absence of sedative premedications recovery of consciousness, as judged by the patient's ability to answer simple commands, from the 5 mg/kg dose begins after 3–4 minutes from injection and is usually complete between 5–6 minutes by clinical assessment. After this time an out-patient may be expected to leave the operating table without assistance and walk to the waiting room. Following a dose of 10 mg/kg, without premedication, recovery again begins after 3–4 minutes (the mean average time is longer), but completed recovery may be delayed up to 10 or 12 minutes. Subsequently there is no hangover or euphoria and the patient feels normal. Of the ten patients in whom intravenous transfusion of FBA.1420 was attempted as the sole general anaesthetic, seven required no adjuvant drugs and these recovered consciousness within 5 minutes of stopping the drip. Assessment of complete recovery was not considered useful in these few cases due to the use of premedicants. Work is now in progress to analyze recovery from FBA.1420 as compared with that from thiopentone and methohexitone, using the performance task experiment suggested by Green and colleagues (1963).

Respiratory system.

Following or just preceding the onset of narcosis a hyperpnoeic phase develops, lasting usually up to 30 seconds. This may be particularly marked after doses of 10 mg/kg. Following this period of respiratory stimulation a phase of respiratory depression sets in, which is associated with occasional apnoea after doses of 5 mg/kg but which may result in apnoea of up to 1 minute after doses of 10 mg/kg. The severity of respiratory depression does not appear to be related to the type of premedication used nor to the degree of hyperventilation (E. Harnik, personal communication, 1963), which suggests that this is a central action of the drug itself and not exclusively due to a lowered level of carbon dioxide in the arterial blood which presumably occurs during previous hyperpnoea. Of the ten patients who were given FBA.1420 by intravenous infusion, two developed periodic respiration of the Cheyne-Stokes type.

Cardiovascular system.

Blood pressure was measured every half-minute by standard brachial sphygmomanometry in 150 patients of whom eleven were hypertensive. Coincident with the loss of consciousness, a fall in blood pressure begins. This fall is mainly systolic and a 30 per cent drop from the resting blood pressure by the end of the first minute may be regarded as usual. The level is restored to within 10 per cent normal over 2–3 minutes, in the absence of other anaesthetic agents. Tachycardia is usually associated. A hypertensive subject shows a greater fall in blood pressure and the recovery to within 10 per cent of the pre-anaesthetic level is slower. The onset of hypotension occasionally precedes the hyperpnoeic phase so that the latter cannot be regarded
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as an autonomic reflex resulting from hypoten-
sion.

In twenty-five patients serial electrocardio-
graphic recordings were taken before, during
and following anaesthesia. The standard three
limb leads and six chest leads were used and
recorded on a direct-writing hot-wire portable
apparatus. No significant changes attributable to
the drug were evident. One patient who also
received halothane developed temporary atrio-
ventricular block.

Haematological and hepatotoxic study.

In a follow-up of twenty-five patients up to the
time of writing, no significant changes in the
result of routine haematological tests were found
that could be attributed to the drug. A study of
blood-clotting mechanisms showed no evidence
of interference. No significant hepatotoxic effects
were found using serum transaminase and
alkaline phosphatase tests.

Side effects and complications.

In the series of 550 patients there has been no
occurrence of laryngospasm or bronchospasm
and marked involuntary muscle movements have
been rare. Hiccough following induction has not
occurred with doses of 5 mg/kg. With doses of
10 mg/kg there was an overall incidence of 8 per
cent although in a separate series another anaes-
thetist reported an incidence of 50 per cent in
patients undergoing minor gynaecological pro-
cedures following atropine only as premedica-
tion. In two patients hiccough appeared after a second
dose of 5 mg/kg following the initial dose of 10
mg/kg. Six patients developed coughing follow-
ing induction. Accidental subcutaneous extrava-
sation occurred in six patients without evidence
of necrotic changes. Red indurated swellings
appeared, however, which although alarming in
appearance, were not painful and resolved com-
pletely within 2 days. Up to the completion of
500 cases only three patients developed thrombo-
phlebitis, which is surprisingly small compared
with that from G.29.505, as observed by Wright
and Payne (1962), Swerdlow (1962) and Riding
and associates (1963).

No nausea or vomiting has followed the use of
the drug as sole agent and salivation has not
presented problems in the non-atropinized out-
patient. Yawning which precedes the hyperpnoeic
phase is an occasional accompaniment of induc-
tion.

Analgesic action.

It was expected that FBA.1420 would not suffer
from the disadvantages of antanalgesia associated
with the barbiturate group. Dundee (personal
communication, 1963), on the basis of analgesi-
metric studies, reported that FBA.1420 possessed
some analgesic properties. Using the drug as sole
anaesthetic for surgery in out-patients there was
no consistent evidence of effective clinical anal-
gesia. On two occasions when FBA.1420 was
given as the sole anaesthetic by continuous intra-
venous infusion following sedative premedica-
tion, complete analgesia seemed to have been
achieved while the patient was maintained at
light narcotic level as judged by the intermittent
appearance of a corneal reflex. A radical mastec-
tomy was performed in one patient and 3.5 g
was given. The other underwent inguinal hernior-
rhaphy, approximately 3 g being used. The
other three patients who were given the drug by
intravenous infusion developed active protective
reflexes from surgical stimulation, and supple-
mentation using nitrous oxide, oxygen and
halothane was needed to achieve satisfactory
operating conditions. In unpremedicated out-
patients, orthopaedic manipulations and reduc-
tions of Colles fractures were satisfactorily per-
formed under FBA.1420 alone but the incision
of abscesses provoked brisk protective reflexes.

During the trial it was discovered that
FBA.1420 had a local analgesic effect. It was the
custom for some time to raise a small intravenous
skin weal with a miniature needle prior to the
insertion of a large intravenous needle. This
manoeuvre was especially useful for introducing
a Mitchell needle. The drug was also effective on
mucous membranes and was comparable to the
effect of 2 per cent lignocaine. The analgesia pro-
duced by intracutaneous and subcutaneous
deposition lasted for many hours and possibly
contributes to the lack of pain associated with
accidental extravasation.
Blood pressure and muscle twitch tracings recorded from anterior tibialis muscle of the cat. The effects of a small dose of 12 mg of FBA.1420 and a standard dose of 25 mg can be seen. A slight increase in twitch may be detected more noticeably after the 25-mg dose.

Suxamethonium 200 μg administered intravenously every 10 minutes to the preparation. The effect on blood pressure and muscle twitch is shown. Preceding the last suxamethonium injection a 25-mg dose of FBA.1420 was given, and this is seen to reduce the twitch depression and shorten the recovery time. Note that muscle temperature is controlled.

These tracings show that there is no post-tetanic facilitation.
Use of FBA.1420 with other Anaesthetic Agents.

The introduction of inhalational agents is conveniently hastened by the hyperpnoeic phase and can be continued by manual inflation during the hypopnoeic or apnoeic phase. By these means satisfactory maintenance of anaesthesia with halothane and even methoxyfluorane can be achieved before the recovery from the induction agent. The drug is freely miscible with most water-soluble agents, for example, gallamine, tubocurarine, atropine, pethidine, dihydrocodeine.

Muscle relaxants.

Suxamethonium. Dundee first reported that FBA.1420 potentiated the action of suxamethonium (personal communication, 1963). His conclusion was based on clinical observations on respiration. Clinical evaluation of this phenomenon at the Royal Free Hospital has tended to confirm a potentiation of respiratory depression. Although the majority of patients recover from apnoea within the normal range of times (say, 3 to 6 minutes), in a few recovery may be delayed for as long as 10 minutes from injection. The mean recovery time certainly appears longer than that following suxamethonium when used in conjunction with barbiturates. The authors are well aware, however, that these observations are fraught with confusion arising from altered gas tensions and the use of artificial ventilation during the apnoeic period. There is no evidence as yet to suggest that this interaction occurs at the neuromuscular junction. On the contrary, neuromuscular studies on the anterior tibialis muscle of the cat showed that FBA.1420 has a slight antagonistic action on the depolarization block produced by suxamethonium (figs. 1 and 2). There was no question of non-depolarizing block conversion (figs. 3 and 4). In a male adult volunteer the muscle endplate was studied by limb electromyography comparing coincident action of suxamethonium with thiopentone and FBA.1420 on two occasions. The results were similar to those of the cat experiments—there was no endplate potentiation of suxamethonium by FBA.1420. The duration of respiratory depression caused by suxamethonium, however, was about twice as long during the FBA.1420 trial as compared with thiopentone.

Non-depolarizing agents. Neither tubocurarine nor gallamine appears to have an interaction with FBA.1420. Mixing it with these drugs at the induction stage of anaesthesia, however, sometimes produces a confusing picture of hyperpnoea competing against neuromuscular respiratory paralysis. It may well be argued that recovery from FBA.1420 is too rapid to make endotracheal intubation under competitive (non-depolarizing) relaxants a wise procedure, due to their slow onset of action compared with suxamethonium, unless additional doses of the narcotic are given.

Intravenous barbiturates. The concurrent use in the same patient of FBA.1420 with barbiturates is uneventful.

DISCUSSION

As a result of this preliminary clinical study the authors feel that FBA.1420 may find a useful place in anaesthesia. The only reservation lies in the unpredictable degree of post-hyperpnoeic respiratory depression following doses in excess of 5 mg/kg and a similarly unpredictable apnoea when the drug is used concurrently with suxamethonium. The low incidence of thrombophlebitis was a reassuring feature. The small liver function study suggests that the drug is not significantly hepatotoxic, but a further carefully controlled trial would seem to be indicated.

The outstanding feature of this new agent lies in its short duration of action. It seems particularly appropriate for short anaesthesia in ambulant patients and as an induction agent for anaesthetics where rapid recovery is indicated. The only real anxiety that has been caused in routine in-patient anaesthesia is that attributable to its brief action.

Whereas doses of 5 mg/kg were generally found to be adequate for the induction of anaesthesia, a higher dosage is recommended as being more useful, especially for out-patients as the sole agent. Analgesia from FBA.1420 was variable and unpredictable. In out-patients needing any-
thing but brief surgery, anaesthesia is better supplemented with nitrous oxide and oxygen following small induction doses of the drug.

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