PROPOFOL AS AN I.V. ANAESTHETIC INDUCTION AGENT IN VARIEGATE PORPHYRIA

P. N. MEISSNER, G. G. HARRISON AND R. J. HIFT

SUMMARY

The choice of an i.v. anaesthetic induction poses problems for the anaesthetist confronted with a patient with one of the acute porphyrias. We undertook a prospective clinical trial in 13 variegate porphyric subjects using propofol as an anaesthetic induction agent. Urinary porphin precursors and porphyrins were measured before operation and 1–5 days after operation. Stool and plasma porphin concentrations were measured over the same period. Comparison of these data in the porphyric patients and in 21 control subjects over the trial period revealed no significant change in porphin or porphin precursor output after operation. Urinary porphin precursor concentrations did not exceed the limits established for variegate porphyric patients in remission, and there were no changes in the stool and plasma porphin profiles or any symptoms of an acute porphyrific attack. We conclude that propofol did not appear to be porphyrinogenic when used for the induction of anaesthesia in 13 patients with variegate porphyria.

KEY WORDS

animal experiments also suggests porphyrinogenicity [10, 11]. Ketamine has shown no evidence of porphyrinogenicity in animal models, even after 6 h of infusion in the diethoxycarbonyldihydrocollidine (DDC)-primed rat model [11], but, even though it possesses excellent analgesic properties, it has other drawbacks which preclude its use as a routine induction agent.

Propofol, the most recently introduced i.v. agent, possesses many of the properties which characterize the ideal anaesthetic agent [12] and in addition, porphyrinogenicity could not be demonstrated in a rat model [13]. We report here a prospective controlled trial of propofol as an i.v. anaesthetic induction agent in porphyric subjects.

PATIENTS AND METHODS

We studied porphyrinic subjects (ASA grades I and II; aged 16–65 yr; normal renal function) requiring general anaesthesia for elective surgery who presented to the participating anaesthetists during a period of 1 year. As far as could be ascertained, no patient had been exposed to any porphyrinogenic drugs in their recent clinical history (past 6 months). Patients excluded from the study were those with severe underlying disease, an allergy to propofol, previous adverse experience with general anaesthesia, those undergoing operations on bladder or bowel, and those who were pregnant. These exclusion criteria were designed to ensure that there were no circumstances that could have an influence on the measurement of excreted porphyrins or precursors, or on porphyrin metabolism generally.

The diagnosis was confirmed in each patient by the demonstration of diagnostic changes in stool, urine and plasma concentrations of porphyrin. A control group was recruited consisting of people without a history of porphyria and in whom porphyrin analysis was normal. All subjects gave written, informed consent.

No restrictions were placed on the anaesthetic procedure except that induction should be with propofol and that porphyrinogenic drugs should be avoided thereafter. The mean induction dose of propofol administered to the 13 patients was 2.45 mg kg⁻¹ (range 1.6–3.33 mg kg⁻¹). Thereafter, 10 received halothane and three enflurane. Atracurium or suxamethonium was used for muscle relaxation and fentanyl, alfentanil and morphine for analgesia. Patients were observed...
for any clinical symptoms suggestive of the acute attack for up to 5 days after anaesthesia and were asked to report any untoward developments thereafter.

Random specimens of urine were obtained before operation (day 0) and on days 1, 3 and 5 after operation. Stool and plasma specimens were obtained also, wherever possible, on the same days. All specimens were protected from light to avoid spontaneous interconversion or photodegradation of the precursors or porphyrins.

ALA and PBG were measured by an established ion-exchange technique [14] using test kits (Biorad, Munich, West Germany). Urinary, stool and plasma porphyrins were extracted, esterified, separated by thin-layer chromatography and measured by fluoroscanning, according to established methods [15-17]. Urinary concentrations of precursor and porphyrin were expressed as µmol/10 mmol creatinine and nmol/10 mmol creatinine, respectively, to take account of variability in urinary concentration. Changes in concentration of precursor or porphyrin excretion between days 0 and 1, 0 and 3, and 0 and 5 were calculated. Data from each individual patient were examined to assess whether values remained within the range of values for non-acute VP. The significance of any variation in porphyrin, ALA or PBG concentration from day 0 to day 1, 3 or 5 was assessed with Student's t test (two-tailed). Similarly, variations in the VP group were compared with those in the control group, as were changes in the porphyric subjects' urinary concentrations of precursor and porphyrin from day 0 to days 1, 3 and 5 compared with those in the control group.

### RESULTS

It has been held traditionally that subjects with VP have normal urinary concentrations of ALA and PBG during remission. We have become aware that this is not so. We therefore redefined our normal ranges (mean, 2 SD) separately for a group of 221 subjects with VP known to be free of acute symptoms, and 93 non-porphyric subjects. These data were drawn from results from our laboratory over the past 5 years. The redefined normal ALA and PBG upper limits for VP subjects free of acute symptoms were 78 and 55 nmol/10 mmol creatinine, respectively. The upper limits for non-porphyric subjects were 40 and 14 µmol/10 mmol creatinine, respectively.

### Subjects

Only patients with VP, the most prevalent form of porphyria in South Africa, presented for surgery during the study period. Thirty-one subjects believed by their physicians to have VP were enrolled. Twelve were excluded because biochemical evidence of porphyria was lacking or because data were incomplete. A further six were excluded from analysis because, despite an abnormal porphyrin profile, the diagnosis was not established beyond doubt. In most instances this was where the diagnosis rested on a mild increase in faecal excretion of protoporphyrin alone. Thus data were obtained for 13 subjects with unequivocal VP. These were compared with 21 control subjects.

### Table 1. Urinary ALA, PBG and total porphyrin (TP) concentrations (mean (SD))

<table>
<thead>
<tr>
<th>Group</th>
<th>ALA concn (µmol/10 mmol creatinine)</th>
<th>PBG concn (µmol/10 mmol creatinine)</th>
<th>TP concn (nmol/10 mmol creatinine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol controls (n = 21)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>9.8 (5.8)</td>
<td>5.0 (3.9)</td>
<td>55.3 (50)</td>
</tr>
<tr>
<td>Day 1</td>
<td>8.9 (5.2)</td>
<td>5.0 (3.8)</td>
<td>63.8 (40)</td>
</tr>
<tr>
<td>Day 3</td>
<td>10.7 (4.6)</td>
<td>3.9 (2.4)</td>
<td>56.8 (39)</td>
</tr>
<tr>
<td>Day 5</td>
<td>11.7 (2.0)</td>
<td>3.5 (2.3)</td>
<td>70.5 (58)</td>
</tr>
<tr>
<td>Propofol VP (n = 13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>24.1 (12.9)</td>
<td>9.6 (7.4)</td>
<td>285 (243)</td>
</tr>
<tr>
<td>Day 1</td>
<td>26.8 (15.6)</td>
<td>11.4 (10.1)</td>
<td>371 (424)</td>
</tr>
<tr>
<td>Day 3</td>
<td>21.3 (12.4)</td>
<td>6.6 (3.9)</td>
<td>128 (70)</td>
</tr>
<tr>
<td>Day 5</td>
<td>24.4 (9.6)</td>
<td>9.1 (7.8)</td>
<td>277 (257)</td>
</tr>
<tr>
<td>Normal population (n = 97)</td>
<td>14.0 (12.7)</td>
<td>5.2 (4.4)</td>
<td>112 (110)</td>
</tr>
<tr>
<td>Non-acute VP population (n = 228)</td>
<td>29.3 (27.6)</td>
<td>8.1 (23.6)</td>
<td>473 (924)</td>
</tr>
</tbody>
</table>

*Fig. 2. Fluctuation of the mean (SD) urinary concentration of ALA for the control (□) and porphyric (■) groups. Individual values fell within the upper limits of "normal" for each respective group at all times.*
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Figure 3. Fluctuation of the mean (SD) urinary concentration of PBG for the control (S) and porphyric (■) groups. Individual values fell within the upper limits of "normal" for each respective group at all times.

The mean concentrations of ALA, PBG and porphyrin in the porphyric patients were greater than those in the control group at all times (table I), including day 0 (P < 0.001), but ALA and PBG concentrations did not exceed the limits established for VP patients in remission (figs 2, 3). No significant increase in output of porphyrin or porphyrin precursor over the baseline was found after operation (P > 0.1); the porphyric group behaved similarly to the control group in this respect. The mean urinary concentrations of total porphyrin of the porphyric group varied greatly and were greater than those of the control group (fig. 4). Again, the change from day 0 to the postoperative days was not significant. No change in pattern of excretion of urinary porphyrin to the earlier haem pathway intermediates was demonstrated by thin-layer chromatography (data not shown). Such a shift would be expected if the pathway were stressed. There were no changes in stool and plasma porphyrin profiles (data not shown).

No symptoms suggestive of an acute attack of porphyria were noted in any subject at any stage.

Figure 4. Fluctuation of the mean (SD) urinary concentration of total porphyrin (TP) for the control (S) and porphyric (■) groups. The concentrations in the porphyric group are high, indicative of the underlying porphyrinic status of the VP patients.

DISCUSSION

To be considered safe for use in the acute porphyrias, ideally a drug should meet the following criteria: first, it should not cause increase in production of porphyrin or porphyrin precursor, and should not induce ALA synthetase or diminish free haem concentrations in laboratory test systems, including various types of cell culture [6, 18-20] and laboratory animals rendered porphyric by the administration of agents such as DDC [6,9,21,22]; second, the drug should be devoid of porphyrinogenic potential in human subjects—its administration should not be followed by symptoms of the acute attack or by a significant increase in excretion of porphyrin and precursor. Such data are usually derived from personal experience, anecdotal evidence or from individual case reports. Few, if any, drugs have had porphyrinogenicity tested prospectively in controlled trials in porphyric patients. Thus doctors must often base their decision to use a particular drug in a porphyric subject on incomplete or possibly inaccurate data. Also, experience in human subjects and laboratory testing sometimes give conflicting results [6, 8, 23].

Propofol has been reported not to induce hepatic ALA synthetase in the rat [13] and therefore, by implication, to be non-porphyrinogenic, but it induces hepatic ALA synthetase in DDC-primed chick embryos [20 and personal communication, Deybach JC]. However, this system is considered by some to be extremely sensitive and may produce seemingly false positive results [6]. There have also been conflicting reports on its safety in humans. In one study, propofol was used to induce anaesthesia in a patient with AIP with apparent safety [24], whereas another case report indicated that urinary concentrations of porphyrin and PBG increased in a VP patient anaesthetized with propofol [25]. However, this patient had been exposed to several anaesthetics over a few days, including an infusion of propofol, and the changes in concentrations of...
porphyrin and PBG were unconvincing [26, 27]. The patient did not experience acute symptoms. This study represents a clinical trial undertaken to assess the safety of propofol for the induction of anaesthesia in patients with an acute porphyria. The lack of significant increase in concentrations of ALA and PBG following administration of propofol suggests that the drug has low porphyrinogenic potential in porphric subjects, at least when used in the dose and manner reported here. This is supported further by failure to alter the urinary, stool and plasma profiles of porphyrin either quantitatively or qualitatively. No symptoms suggestive of the acute attack were noted. We conclude, therefore, that propofol, as used for the induction of anaesthesia in 13 patients with VP, did not appear to be porphyrinogenic. However, the number of patients studied was small and the disease is unpredictable, so care should always be taken when using any drug in porphyria. We cannot extrapolate our findings to the use of propofol for maintenance of general anaesthesia by continuous infusion until further clinical experience has been obtained. In the light of the case report referred to above [25], we suggest that caution be exercised with propofol for this purpose.

Comment is necessary on the choice of halothane for maintenance of anaesthesia in this study. Two reports and some experimental data warn of its risk in porphric patients [7, 20, 28], but this conflicts with other experimental data [10] and much clinical experience accumulated by our and other units, where it has been used safely in porphric patients on numerous occasions. As 10 of our patients received halothane, this study presents substantial evidence that halothane, in addition to propofol, may be used safely in the acute porphyrias.

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