NIVALIN (GALANTHAMINE HYDROBROMIDE), AN ADDITIONAL DECURARIZING AGENT. SOME INTRODUCTORY OBSERVATIONS

BY

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SUMMARY

Galanthamine hydrobromide (Nivalin), an alkaloid from the bulbs of snowdrops, is widely used in Bulgaria as an antagonist to non-depolarizing muscle relaxants. The pharmacology is reviewed and experiences in the use of galanthamine in 24 patients are described. It is about one-tenth as potent as neostigmine. As changes in pulse rate and blood pressure were slight, it is rarely necessary to inject atropine before galanthamine. Salivation had to be suppressed by means of atropine in one-seventh of the cases. Detailed investigations are suggested.

When using non-depolarizing muscle relaxants it is common practice to give antagonists either routinely after each curarization or, at least, when tidal exchange at the end of anaesthesia is inadequate. But just as the perfect anaesthetic agent is still being searched for, so the drugs used for reversal of neuromuscular block are not yet ideal. Neostigmine causes bradycardia, and increases salivation and bronchial secretion, unless preceded by atropine, and may in large doses act itself as a blocking agent. Intravenous atropine raises the pulse rate and may be followed by dangerous arrhythmias (Eger, 1962; Gottlieb and Sweet, 1963), and cardiac arrest has been described after both (e.g. Lawson, 1956; Gray and Wilson, 1959; Dinnick, 1964). Edrophonium is too short-acting to prevent recurarization.

It was of interest, therefore, to investigate a long-acting anticholinesterase agent, widely used in Bulgaria, namely galanthamine hydrobromide (Nivalin), which can be given without atropine in most cases and is reported to be of low toxicity.

PHARMACOLOGY

Galanthaminum was isolated in 1952 by Proskurnina and Areshkina from tubers of Galanthus woronovii, found in the Caucasus, and in 1956 by Paskov and Iwanova-Bubewa (quoted from Stojanov, 1964a) from the bulbs of snowdrops, Galanthum nivalis. It is a phenantridine derivative, with the structural formula shown in figure 1. Its anti-tubocurarine action was first described by Mashkovskii (1955).

The hydrochloride inhibits the acetylcholinesterase of muscle and the cholinesterase of plasma and brain, affecting the muscle enzyme more than pyridostigmine but less than neostigmine (Irwin and Smith, 1960a). In the mouse the toxicity of the hydrobromide, compared to neostigmine, is 16.5 times less after intravenous injection, and 21.3 times less when given intraperitoneally (Boissier, Combes and Pagny, 1960).

Its antagonism to non-depolarizing relaxants is one-tenth that of neostigmine; it acts faster but the effect is of shorter duration. It prolongs the action of suxamethonium (Cheymol et al., 1964). Bradycardia is caused in frog, rabbit and dog, and hypotension in the dog. Galanthamine enhances the acetylcholine-provoked contraction of smooth muscle and increases the contraction of striated muscle after maximal direct and indirect stimulation. It stimulates the cerebral cortex, as shown by the electroencephalogram and excites bulbar and spinal reflexes (Bretagne and Valetta, 1965). Given subcutaneously, the effect of galanthamine is somewhat inferior to, and slower than, neostigmine but longer-lasting and less toxic (Pestel, 1961).

On investigation of galanthamine and related compounds it was found that the methiodide, a quaternary amine, is more potent than the non-quaternary hydrobromide (Irwin and Smith, 1960b), being about four times as powerful (Boissier and Lesbros, 1962).
Paskov, Dobrev and Nikoforov (1964), in experiments in cats and rabbits, showed that galanthamine is an effective antagonist to morphine-induced depression of the central nervous system and respiratory centre. Respiratory depression, caused in these animals by hydroxydione, could also be counteracted (Stojanov, Dobrev and Paskov, 1965). The L.D.₉₅ in rats is 45 mg/kg, in rabbits 12 mg/kg and in cats 60 mg/kg (Stojanov, 1964a).

Stoyanov and Vulchanova (1963) reported on the use of galanthamine as a decurarizing agent in more than 2,000 patients, drawn from all parts of Bulgaria. Later, experiences in 478 personal cases were reviewed by Stojanov (1964a). Spirographic studies in 50 patients were also reported (Stojanov, 1964b). By 1966, 6,000 patients had received this drug at the Sofia University Hospital alone (Stojanov, 1966, personal communication, who also stated that its action in man lasts for about 2 hours). Bretagne and Valetta (1965), in France, used it successfully in 50 patients.

**METHODS AND MATERIAL**

Galanthamine was used in 24 of 27 consecutive cases who required muscular relaxation, the latter being the only criterion for inclusion in the trial. Premedication varied according to the condition of the patient but all received atropine or hyoscine. Anaesthesia was induced with thiopentone and the trachea was intubated with a cuffed tube after suxamethonium injection and inflation of the lungs with oxygen. Anaesthesia was maintained with increments of thiopentone, nitrous oxide (4 l./min) and oxygen (2 l./min) with or without pethidine. In one patient, halothane was added to the inspired gases after 50 minutes in order to avoid excessive dosage of thiopentone. The relaxants used were tubocurarine (12 cases), diallylnortoxiferine (10) and gallamine (2). One patient, in whom tubocurarine 14 mg sufficed for 2½ hours, was given gallamine 20 mg for peritoneal closure. Tubocurarine doses ranged from 10 to 41 mg, diallylnortoxiferine from 9 to 23 mg. Ventilation was manually controlled using a circle circuit with carbon dioxide absorption.

Before injection of galanthamine, manual ventilation was stopped for a period of about 2 minutes in order to observe and measure the depth of spontaneous respiration if this had returned. The absorber was left in circuit during this period. In the first three cases, when atropine was given before galanthamine, there was a further test for spontaneous breathing between the two injections. Respiration were measured with a Dräger Volumeter. The pulse rate was counted by palpation and the blood pressure was measured by auscultation or palpation.

Galanthamine was at first injected intravenously in doses of 5 mg but when this proved to be insufficient, and when pulse and blood pressure were found to remain steady, the dose was increased to 10 mg. Reactions were observed up to 5 minutes before further doses were added.

There were 17 female patients (ages 14–62) and 7 males (ages 13–61). Body weights ranged from 36 to 94 kg. The operations performed were:

- Gynaecological laparotomy 9
- Gynaecological vaginal operation 3
- Subtotal gastrectomy 3
- Appendectomy 5
- Urogenital 3
- Skin graft 1

Three out of the 27 cases were excluded because ample spontaneous respiration had returned when the testing was about to begin.

The duration of anaesthesia varied from 39 to 247 min.

**RESULTS**

**Respiration.**

In 20 of 24 patients there was an increase in respiratory volume within 4 minutes of injection of galanthamine 10 mg; 15 patients received a second dose of 10 mg, and 4 a third, also of 10 mg. To raise the tidal volume to 200–400 ml a dose of 20 mg was usually needed. Apart from periodic manual ventilation during the reversal period, to avoid hypoxia, no measures were taken to improve tidal exchange. All patients were returned to the ward awake and with clinically satisfactory respiratory excursions.

**Pulse rate.**

There was no change in pulse rate in 7 cases, a rise in 6 and a fall in 11. Rises of up to 16 beats/min and falls not exceeding 20 beats/min were noted. In 6 cases the rate declined by 4 beats/min only and in 2 by 20 beats/min. The lowest rate observed was 68 beats/min, after a fall of 20 beats/min; as the pre-anaesthetic rate had been 76 beats/min, atropine was not considered necessary for this patient, nor for another whose rate fell from 100 to 80 beats/min.
Blood pressure.
No change occurred in 7 patients. There was a rise in 10 and a fall in 6. In one patient it was not measured. The rises ranged between 5 and 15 mm Hg. The steepest drop, from 110 to 90 mm Hg, was noted in the patient whose pulse rate declined to 68 beats/min. In one patient the pressure fell from 235 to 220 mm Hg. In the remaining 4 the pressure fell 5 or 10 mm Hg.

Salivation.
Secretions were not obviously increased in 16 patients, somewhat increased in 2, and greatly increased in 6 of whom 3 required intravenous injection of atropine 0.6 mg (one of these was a heavy smoker).

Awakening.
Patients awoke very promptly after galanthamine, so much so that in preliminary trials respiratory volume measurements could not be made when the drug was given at the moment when nitrous oxide was discontinued. Subsequently nitrous oxide administration was continued until the effect of the first injection of galanthamine had been observed. Within 2 minutes of discontinuing anaesthesia most patients opened their eyes on being called by name. They would obey commands, open their mouths or put out their tongues. The return to complete wakefulness was often striking, the patients making remarks such as: “I feel cold”; “My belly hurts”; “Shall I survive?” One Arab patient, after Caesarean section asked immediately in Hebrew, of which she knew but a few words: “Have I got a son?” (a vital question with all our oriental communities), being sufficiently conscious at this stage to speak in a foreign language.

Muscular power.
The return of grip strength and of the ability to lift the head sometimes was not as rapid as the return of wakefulness or the recovery of respiration. Even when a volume of 500–800 ml could be exhaled into a mask on being requested to breathe deeply, and when thoracic and abdominal respiration were fully co-ordinated, the head could hardly be lifted and/or the hand grip was weak. In one case, after 160 mg gallamine, whilst the patient could expel 300–400 ml into the mask he could not lift his arms at all, and complained of it as soon as he opened his eyes. His grip strength was still reduced after half an hour, whilst respiration remained satisfactory.

Side effects.
The same patient, the only one, sweated and salivated profusely, suction of the nasopharynx being necessary. Transient erythema of the trunk was observed in one patient; there had also been reddening around the site of the initial thiopentone injection which had disappeared before the end of anaesthesia. No other side effects were observed, nor were there any signs of recurarization.

Two protocols on the effect of galanthamine are shown in table I.

DISCUSSION
The manufacturers of galanthamine (Chimpharm) recommend for adults a dose of 10–20 mg. Stojanov (1964a) begins with 5–10 mg, repeating it, if needed, after 5–10 minutes. In our experience a dose smaller than 10 mg is not effective in an adult and more often 20 mg is required. Stojanov does not mention the doses of tubocurarine and gallamine used and, therefore, the findings may not be comparable. Bretagne and Valetta (1965) consider that 15 mg is a suitable dose to reverse the effect of doses of tubocurarine of up to 40 mg and that 20 mg should be given when the dose of tubocurarine has exceeded 40 mg. In the present series the impression was gained that galanthamine requirements depended not only on the dose of relaxant and on the interval between injections of blocking agent and antagonist (Bretagne and Valetta, 1965), but also on the presence or absence of spontaneous respiration before reversal is attempted.

As the potency of neostigmine is considered to be ten times as great, 25 mg of galanthamine could be expected to be an average dose. Stojanov (1964a) gave 30–40 mg in a few cases; in the series described here the maximum dose was 30 mg and was used in 4 patients. With an anaesthetic technique utilizing moderate degrees of curarization, and with the last dose of relaxant having been given a considerable time before the end of anaesthesia, the writer’s doses seemed adequate. Whether they would suffice after mechanical ventilation, with full curarization until near the end of anaesthesia, remains to be tested.
TABLE I

Female, 44 yr; fibroid uterus; total hysterectomy.

<table>
<thead>
<tr>
<th>Time in min, relating to galanthamine, 1st dose</th>
<th>Dose (mg)</th>
<th>Tidal volume (ml)</th>
<th>Blood pressure (mm Hg)</th>
<th>Pulse (beats/min)</th>
<th>Anaesth. time 2 hr. 41 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>−7</td>
<td></td>
<td>40–60</td>
<td>155/100</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>−1</td>
<td></td>
<td>40, once 80</td>
<td>165/100</td>
<td>104</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>10</td>
<td></td>
<td>165/100</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>+1</td>
<td></td>
<td></td>
<td>165/100</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>+3</td>
<td></td>
<td>120–150</td>
<td>150 syst.</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>+5</td>
<td></td>
<td>120–150, once 200</td>
<td>165 syst.</td>
<td>108</td>
<td>Strains on tube, opens eyes</td>
</tr>
<tr>
<td>+8</td>
<td>10</td>
<td>400</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>+10</td>
<td></td>
<td></td>
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</tbody>
</table>

No increased salivation.

Male, 29 yr; acute appendicitis; appendicectomy.

<table>
<thead>
<tr>
<th>Time in min, relating to galanthamine, 1st dose</th>
<th>Dose (mg)</th>
<th>Respiratory volume (ml)</th>
<th>Blood pressure (mm Hg)</th>
<th>Pulse (beats/min)</th>
<th>Anaesth. time 1 hr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>−3</td>
<td></td>
<td>Irregular, about 20</td>
<td>105</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>8</td>
<td>About 150</td>
<td>120–140</td>
<td>105</td>
<td></td>
</tr>
<tr>
<td>+1</td>
<td></td>
<td>120–150</td>
<td>80</td>
<td></td>
<td>Anaesth. off</td>
</tr>
<tr>
<td>+4</td>
<td>8</td>
<td>Up to 300</td>
<td></td>
<td></td>
<td>Opens eyes</td>
</tr>
<tr>
<td>+6</td>
<td></td>
<td>Up to 300</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+7</td>
<td></td>
<td>Up to 500</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+9</td>
<td></td>
<td>More than 500</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+12</td>
<td></td>
<td></td>
<td>110</td>
<td>108</td>
<td></td>
</tr>
</tbody>
</table>

Much salivation; atropine 0.6 mg given. Patient could not lift his head, but could blow 800 ml into mask when asked. A further 10-mg dose of galanthamine, 20 minutes after the first injection, made little difference to the ability to lift the head; this gradually recovered spontaneously.

When judging the effect of galanthamine, given in divided doses over a period of time, one has to bear in mind that the relaxant may have been partly metabolized and/or excreted meanwhile. In 4 patients in whom the effect was only slight, satisfactory respiration might have returned had nothing but aided ventilation been given during the period of waiting. In order to distinguish between the effect of repeated doses of galanthamine and the “natural” waning of the neuromuscular blocking effect of the relaxant more observations will be necessary. In spite of the few relative failures, however, there was no doubt about the decurarizing effect of the agent.
The decisive advantage of galanthamine over neostigmine, in the writer's view, is that atropine is not necessary in most cases. Stojanov (1964a) gives it to patients with pre-operative bradycardia; Bretagne and Valetta (1965) do not mention it. In the present series atropine was required after galanthamine to suppress salivation but not to counteract bradycardia. It has always seemed incongruous to the author, especially when dealing with patients of advanced age, or suffering from cardiovascular disease, that having endeavoured to maintain a steady pulse rate through hours of anaesthesia, atropine is injected in a dose of 1 mg or more, thus deliberately causing a sudden rise of 20–30 beats/min. At the beginning of this trial 3 patients received atropine before galanthamine; of the remainder only 1 out of 7, all under 45 years, needed atropine 0.6 mg, a dose considered insufficient to suppress the muscarinic effect of neostigmine (Dinnick, 1964).

In 2 cases who received doses of 18 mg and 17 mg galanthamine for the first injection, the pulse rate and blood pressure remained unaffected.

The quick awakening has also been observed by others (Stojanov, 1964a; Bretagne and Valetta, 1965). The apparent discrepancy between awakening and satisfactory respiration on the one hand and residual muscular weakness on the other might be explained by the direct stimulating action on cerebral cortex and respiratory centre (Paskov, Dobrev and Nikoforov, 1964; Bretagne and Valetta, 1965) at a time when the anticholinesterase effect had not fully developed. Measurements of respiratory volume, oxygen-saturation, Pco₂, and pH, taken simultaneously with electromyography and electroencephalography, might determine whether these two effects are indeed separate.

Tubocurarine and diallylnortoxiferine were chosen as the main relaxants because they do not raise the pulse rate as does gallamine. It was also thought that diallylnortoxiferine relaxation might be reversed by smaller doses of galanthamine as is claimed for neostigmine by Venn (1965), though not supported by the findings of Hunter (1964). No difference was observed; complete relaxation by whatever non-depolarizing agent seems to demand full doses of the antagonist.

Stojanov (1964a) describes the use of galanthamine in doses of 5 mg intramuscularly twice daily to stimulate postoperative peristalsis, and of small doses intravenously in paralytic ileus. This effect has not been tested; it would be in keeping with the stimulant action on smooth muscle, as quoted above.

The aim of this report is to introduce galanthamine into English-language anaesthetic literature. Though the number of cases is small, the results show, together with the experiences at other centres, that the preparation is well worth an extensive investigation.

ACKNOWLEDGEMENTS

My thanks are due to Prof. D. Paskov, Head of Institutfi po Farmacologia, Wisch Medicinsky Institut, Sofia, and Chimpharm, Sofia, Bulgaria, for the supply of Nivalin, and to Dr. E. A. Stojanov, Hon. Secretary of the Society of Anaesthesiologists, Bulgaria, for discussing with me his experiences of the drug.

I also have to thank my surgical and gynaecological colleagues at the Shaare Zedek Hospital, Jerusalem, Israel, for their patient waiting between operations while the effects of galanthamine were being studied.

REFERENCES

Lectures on Tape

Sir,—I refer to your editorial in the July 1967 issue (Brit. J. Anaesth., 39, 521), which has just reached me.

Your comments on taped lectures were extremely apposite. Nevertheless, the problems of presentation can be overcome. This is well exemplified by the tapes produced and distributed for the Recording Library of the Royal College of General Practitioners by Drs. John and Valerie Graves. I am sure it is to their work that reference is made in the statement that “considerable progress has already been achieved in the field of general practice”.

Dr. John Graves once described to me the considerable trouble that is taken in the selection of format, the prerecording editing of material and the preparation and rehearsal of the speaker before the microphone in the production of the material for this library.

I found the material invaluable in maintaining my own education and that of my partners in a West Country group general practice. I am sure junior anaesthetists could find a similar service, designed for them, of immense value.

The Ministry and the Faculty could both draw on the experience of the Royal College of General Practitioners in this field. In addition, here in the U.S. there is a service known as Audio-Digest active in this field and new developments applicable to the audio-visual field in the domestic surroundings can be anticipated shortly.

J. L. R. Barlow
Chicago

Corrigendum

Sir,—My attention has been called to a typographical error in the recently published tenth edition of Recent Advances in Anaesthesia (J. & A. Churchill Ltd.). On p. 48, line 3, the dose of phenoperidine is given as 0.5 mg/kg instead of 0.05 mg/kg. The publishers have already arranged for an erratum slip to be pasted into this page but some copies had previously been put into circulation. I would be grateful if you would kindly print this letter so that readers of the book can make the necessary alteration if it has not already been done and thus avoid any risk of possible overdosage.

C. Langton Hewer