THE CLINICAL USE OF LAUDOLISSIN*

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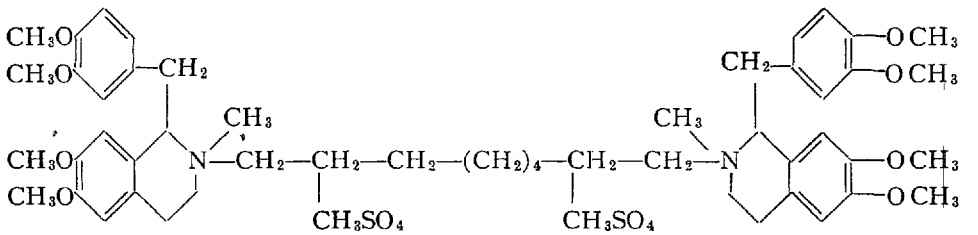
RELAXANT drugs were introduced into clinical anaesthesia twelve years ago. Since that time numerous preparations of this type have been produced for investigation and use by anaesthetists. Some of these have remained as useful additions to the pharmacopoeia, others have not proved acceptable to the practising clinical anaesthetists. Each one has had to be shown to have some characteristic the possession of which makes the use of it under some circumstances more desirable than d-tubocurarine, the relaxant to which all others have been compared.

Laudolissin is a relaxant drug, its particularly attractive qualities being that it is synthetic and that it acts for a considerably longer period than d-tubocurarine.

Our experience with laudolissin has been clinical, but a brief review of the laboratory and clinical findings of other investigators which served as a background to its use will be of interest. The pharmacological activity of laudolissin, also known as Allen and Hanburys' Compound 20, has been studied by Collier, Macauley, Bodman and Taylor who synthesized it (1, 2, 3, 4, 5). Laudolissin is a decamethonium compound with modified isoquinolone groupings at each end of the chain:



Decamethylene bis-[1:2:3:4-tetra hydro-6:7-dimethoxy-1-(3′:4′-dimethoxybenzyl) -2-methylisoquinolinium] dimethosulphate.

The investigations in the laboratory were made on both animals and conscious human volunteers.

1. Laudolissin acted as a curarizing agent, the muscle itself being excitable by direct stimulation while the animal was under a paralyzing dose of the drug.
2. Voluntary muscle was paralyzed without initial stimulation.
3. Neostigmine antagonized laudolissin.
4. The potency of laudolissin in man was one-half that of d-tubocurarine; it was more potent in the rabbit and cat but less so in the mouse and rat.
5. An equipotent dose of laudolissin acted longer than d-tubocurarine, while doses given less than an hour apart might have an accumulative effect.

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6. Small doses of suxamethonium hastened recovery from laudolissin; larger doses caused paralysis followed by more rapid recovery.

7. There was little difference from d-tubocurarine as regards histamine release; if anything, less histamine was released by laudolissin.

8. In animals laudolissin has one-quarter the ganglion blocking effect of d-tubocurarine.

9. Ether acted synergistically; thiopentone had no effect on the toxicity of the drug.

In 1952, Bodman, Morton and Wylie (4) reported a series of 186 surgical cases in which laudolissin had been used. In 1953, Binning(6) reported its use for 100 cases. Our series includes 103 patients.

Laudolissin is dispensed in 1½ cc. ampoules containing 30 mg. of the drug, that is 20 mg. in each cc. As 2 mg. of laudolissin have about the same potency as 1 mg. of d-tubocurarine, for many patients the initial dose of laudolissin was 30 mg., that is, the entire contents of the ampoule. For additional doses it was found useful to dilute the 1½ cc. to 5 cc., thus having 6 mg. of the drug per cc. When laudolissin was given through a needle immediately after thiopentone a heavy, white precipitate formed which on one or two occasions stopped up the needle. With an intravenous running this could not occur. Usually, because of the surgical procedure proposed, the patient required an intravenous infusion which made the administration of the drug easier. The usual sequence of events during induction of the anaesthetic was the administration of thiopentone followed by the maintenance agent of choice and suxamethonium if intubation was considered necessary. If intubation was not required, laudolissin was given at any time after the patient was asleep, but at least five minutes before relaxation was desired, since the effect of the drug was not evident for from two to five minutes after injection. When endotracheal intubation was intended, laudolissin was frequently given immediately after the suxamethonium before intubation was performed, and this proved to be a very successful sequence of events. The laudolissin took sufficiently long to be effective that the suxamethonium effect was over before it was active and neither drug interfered with the benefit of the other.

The only criterion for the use of the drug in these cases was that the operation was expected to last about one hour or longer, although in thirteen instances this did not happen. No other unusual drug was used for the 103 patients in this group. There were 56 females and 47 males, the ages ranging from 13 to 73 years. Seventy-four operations were intra-abdominal, 35 lower and 39 upper; 18 were orthopaedic or neurosurgical major procedures; the remaining patients included some who did not require relaxation but with whom it seemed interesting to use the laudolissin to note its effect in producing a quiet anaesthetic with less than the usual amount of sedative anaesthetic agent over a long period. The pre-operative sedative for the majority of the patients was a combination of morphine and hyoscine.

Thiopentone was used for induction of anaesthesia in all but two cases when the operation was Caesarian section; here cyclopropane was used throughout. In 57 cases cyclopropane was used for maintenance, in 24 thiopentone was continued with nitrous oxide, in 18 thiopentone, nitrous oxide and trilene were

used, and for 4, ether. Forty-three of the patients were intubated using suxamethonium. It was, of course, quite adequate to wait for the optimum relaxation of laudolissin to intubate, 5 patients being done in this way. One man had had an initial 30 mg. of laudolissin followed an hour later by 6 mg. One-half hour after this the cuff of the endotracheal tube broke and reintubation was necessary. The damaged tube was withdrawn and another tube inserted with neither difficulty nor reaction. In the majority of the patients a topical spray was used before intubation. The onset of relaxation due to laudolissin seemed to vary from about two to five minutes, occasionally accompanied by marked respiratory depression, but more often not, and it was only when the abdomen was opened with great ease that the degree of relaxation was apparent, for the respiratory depression usually seemed much less than would have been expected with an equally relaxing amount of d-tubocurarine.

At no time was the surgeon aware that a new relaxant drug was in use, and during eight operations the surgeon commented on the extraordinary relaxation. Only anaesthetists know how difficult it is to refrain from asking about the degree of relaxation, and how readily they are apprised of any deficiency in that respect, so these favourable, unsolicited remarks were much appreciated. In three instances the anaesthetist felt that the operating conditions were only fair, although there were no complaints. One of them was the first case in which the drug was used, and probably the initial dose was not large enough, although intubation had been performed without difficulty under laudolissin. One of the other patients required a deeper anaesthetic, the other satisfied the surgeon but from the anaesthetist's point of view would have been better with more relaxant. It was found that an initial dose of 30 mg. was most successful for an intra-abdominal operation, and provided conditions similar to those given by 15 mg. of d-tubocurarine. Sometimes a smaller initial dose was used, the amount being determined, as is that of any relaxant, by the impression the anaesthetist has of the patient's requirements. In 21 of the 103 cases additional laudolissin was given in the first hour; several of these had had small initial doses, others were having controlled respiration. The maximum amount given was 70 mg., for operations lasting two and one-half and three hours. In several instances only 10 mg. were given when relaxation was not the reason for the use of the drug.

Fifteen patients were seen to require more relaxation for closure of the peritoneum. This was accomplished in several ways to determine the effects produced by various substances on the patient already under laudolissin. Thiopentone was given twice, ether was added three times when it had not been used in the course of the anaesthetic, suxamethonium was added eight times, and laudolissin added twice, all successfully. When ether was added, a few breaths sufficed. On 18 occasions atropine and prostigmine were given at the end of the operation because of respiratory depression, one of the instances being after an additional 10 mg. of laudolissin had been given for closure. Each time the response to the prostigmine was prompt, excellent and permanent. Tensilon was given twice with a good response.

As with other relaxant drugs, respiratory depression was variable, depending on the patient, apparently, rather than on the drug. The general impression was

that the depression was less than it would have been with doses of d-tubocurarine producing the same degree of relaxation. Twenty-seven patients had no respiratory depression. Twenty-one patients had assisted or controlled respiration almost throughout their procedure. Very few of the patients were not reacting on leaving the operating room, and these recovered reflexes shortly after reaching the recovery room. There was one death in the recovery room following a cholecystectomy; the operation had lasted 135 minutes, during which time the patient had had controlled respiration under a total of 60 mg. of laudolissin with nitrous oxide and ether endotracheal anaesthesia. She received 1/100th of a grain of atropine and 5 mg. of prostigmine ten minutes before the completion of the operation and was awake in satisfactory condition on leaving the operating room. Cardiac arrest occurred forty-five minutes after she reached the recovery room. During cardiac massage the heart ruptured at the site of an infarct. It was felt that the laudolissin had had no connection with the death.

There were no post-operative sequelae which were attributable to the use of laudolissin.

During operation, in the great majority of cases, the pulse rate remained remarkably constant, within the normal limits, and the blood pressure also remained fairly constant. Certainly neither pulse nor blood pressure seemed to be affected by the laudolissin. A seriously ill woman had had two previous operations, one recently and one two years before, during which there had been tachycardia and questionable fibrillation. Ether had been used on the second occasion because of the earlier history. It was considered unnecessary and, perhaps, unwise, to pass an endotracheal tube. Following a sleep-producing dose of thiopentone she had, for a four-hour upper abdominal procedure, 40 mg. of laudolissin with cyclopropane. Only twice during that time was her pulse over one hundred and she had intermittant pulsus alternans, for which a procaine drip was added. Her pressure varied within normal limits. This was her least eventful anaesthetic and her course was good.

Another patient had received a thiopentone, curare, demerol, nitrous oxide anaesthetic early in the day for a minor procedure, during which he was very difficult to anaesthetize. When the major procedure for which he was given a thiopentone induction followed by nitrous oxide and trilene and laudolissin was over, his respirations were still depressed. As it was eighty minutes since the laudolissin had been given, it was considered likely that the depression was due to other drugs. Coramine was therefore administered and the respiratory depression was rapidly relieved. The laudolissin had provided excellent conditions for operating on this patient.

For two neurosurgical laminectomies laudolissin was given because the patients were not settling down, and promised to require large quantities of anaesthetic agents. They responded immediately and were carried easily for the duration of the operation without respiratory depression.

For the Caesarian sections, 15 mg. of laudolissin were used with no demonstrable effect on the babies.

From our clinical experiences laudolissin has proved itself a useful drug. When the supply was finished we missed it. There are many operations for which

a longer-acting relaxant than d-tubocurarine is very convenient. We had no electrocardiograms taken during operations, but in three recorded in one of the other clinical series no changes were noted. As with other investigators, we found no evidence of bronchoconstriction, nor was there evidence of haemolysis, thrombosis or phlebitis. We are inclined to agree with them, also, that the antagonistic effect of suxamethonium was not as evident clinically as it was reported to be in animals.

One of our anaesthetists has used laudolissin as the relaxant for eighteen additional patients who received largactil during their surgical procedure. These patients were not included in the above series. There was an impression that largactil potentiates the effect of laudolissin as it has been said to do in the case of other relaxants.

In conclusion it may be said that laudolissin was found a good relaxant of the curare type, lasting much longer than d-tubocurarine and, therefore, being more convenient to use for operations requiring relaxation for an hour or longer. No undesirable side effects were experienced. The fact that it is synthetic means that it should be cheaper and that the supply is not likely to fail.

Dr. R. A. Gordon, Dr. I. M. MacKay and Dr. S. L. Vandewater are to be thanked for undertaking to use laudolissin in a number of cases, and provide records of them and for their personal impressions regarding the drug.

Our thanks are due to Messrs. Allen and Hanburys Company for the supply of the laudolissin.

Summary

Laudolissin is a new synthetic relaxant drug of the curare type, with a duration of action considerably longer than that of d-tubocurarine. In clinical use laudolissin has been found to be more convenient than d-tubocurarine for operations requiring relaxation for an hour or longer. No undesirable side effects were experienced in 103 cases in which the drug was used.

Résumé

La laudolissine est un relâcheur synthétique dont l'efficacité est de plus longue durée que celle de la d-tubocurarine. C'est un composé du décamethonium avec groupements isoquinolones modifiés à chaque bout de la chaîne. La laudolissine agit comme agent curarisant, causant une paralysie du muscle volontaire sans excitation initiale; elle est neutralisée par la néostigmine. Chez l'homme 2 mgm de laudolissine sont aussi puissants que 1 mgm de d-tubocurarine. Des dosages administrés à des intervalles de moins d'une heure peuvent s'accumuler. L'éther a un effet synergique. La laudolissine diffère peu de la d-tubocurarine quant à la libération d'histamine.

La laudolissine s'obtient en ampoules de 1½ cc contenant 30 mgm de la drogue. Un lourd précipité blanc se forme avec le thiopentone. Il faut de deux à cinq minutes pour que la drogue produise le relâchement. On s'est souvent servi du suxaméthonium pour permettre plus tôt l'intubation. L'action de la laudolissine n'était pas changée. On pouvait l'administrer immédiatement après le suxaméthonium mais avant l'intubation.

Les 103 patients de cette série étaient âgés de 13 à 73 ans; 74 subissaient des opérations abdominales, 18 des opérations majeures orthopédiques ou neurochirurgicales, les autres une variété de procédés dans lesquels la laudolissine servait à diminuer la quantité de l'agent anesthésique nécessaire. Vingt et un de ces patients reçurent une quantité additionnelle de laudolissine pendant la première heure. Pour obtenir un relâchement plus profond pour l'occlusion, des quantités additionnelles de laudolissine, d'éther, de thiopentone et de suxaméthonium ont prouvé leur efficacité. Vingt-sept des patients ne témoignèrent aucune dépression respiratoire.

Il y eut une mort dans la série avec laquelle la laudolissine ne semblait pas associée. L'emploi de la laudolissine ne semblait influencer ni le pouls ni la pression artérielle. Aucuns effets secondaires ne se déclarèrent.

Dans les expériences cliniques la laudolissine s'est trouvé être un bon relâcheur du type curare, à durée beaucoup plus longue que la d-tubocurarine et par conséquent plus commode à employer dans les opérations exigeant un relâchement d'une heure ou plus.

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