



The Place of Erythroidines in the History of Neuromuscular Blockers

Alistair G. McKenzie

Department of Anaesthesia, Critical Care & Pain Medicine, Royal Infirmary of Edinburgh, UK



ARTICLE INFO

Article history:

Received 3 September 2018

Received in revised form 13 October 2018

Accepted 29 October 2018

ABSTRACT

Between 1938 and 1951 erythroidine derivatives were seriously considered as alternatives to curare for the provision of muscle relaxation. This has been overlooked in the published history of anaesthesia. The first publication on the paralysing effect of an extract of *Erythrina americana* was in 1877, but this was in a Mexican journal, which was not widely read. Sixty years later erythroidine was isolated, and in 1938 it was first used clinically to treat spastic dystonia, preceding the use of Intocostrin for this purpose. By 1943 dihydro- β -erythroidine was prepared in crystalline form, which was equipotent with curarine and of acceptable duration; it was used in clinical anaesthesia in 1946. In the 1940s curare was presented in solutions with potency stated in units, determined by bioassay, which was a disadvantage compared with the straightforward mg of dihydro- β -erythroidine. However, by the early 1950s, improvement in the pharmaceutical presentation of d-tubocurarine and new neuromuscular blockers, displaced the erythroidines.

© 2018 Anesthesia History Association. Published by Elsevier Inc. All rights reserved.

Introduction

Between 1938 and 1951, erythroidine derivatives were seriously considered as alternatives to curare for the provision of muscle relaxation. As this has been rather overlooked in the published history of anaesthesia, this article seeks to provide a balanced account to fill this gap in the story of neuromuscular blockers.

Methods

An extensive literature review was conducted, including medical, pharmacological, chemical, and biographical.

Results and Discussion

Colorin is the name of a tree native to Mexico, the red seeds of which were known by the Aztecs to be poison, producing paralysis.¹ The tree was classified *Erythrina americana* by P. Miller (1691–1771), but the first publication on the paralyzing effect of an extract (on animals) used the synonym *Erythrina coralloides*.² This was in the March 1877 issue of *Gaceta Medica de Mexico* which was not widely read. The authors, M. Dominguez and F. Altamirano, suggested that the extract attacked the motor nerves like curare.² Altamirano gave the name *erythroidine* to the principle producing this effect, which

was mentioned in a monograph on *Erythrina* in the 20th edition (1918) of *The Dispensatory of the United States of America*, with a suggestion of it being a substitute for curare.³ In 1934, M. Arzac-Behnken completed her thesis at the National University of Mexico on the effects of a liquid (alcoholic) extract of *Colorin* seeds compared with curare. She reported that hypodermic administration of the extract to seven guinea pigs and two dogs produced paralysis, from which they did not recover.⁴ The following year in the Faculty of Medicine at the same institution, E. Ramirez and M.D. Rivero reported a chemical analysis of the drug and reaffirmed its paralysis of motor nerves (in frogs) by chronaxie determinations.⁵ Prompted by these publications and the scarcity of “reliable curare,” in 1936–1937, A. Lehman, a pharmacologist at Stanford University in San Francisco, tested an alcoholic extract of the seeds on animals and opined that this was indeed a promising and relatively easily available substitute for curare.⁴

In 1937, K. Folkers and R.T. Major, working in the research laboratories of Merck & Co. Inc., Rahway, NJ, USA, isolated pure crystals of the alkaloid, for which they retained the name *erythroidine*. They confirmed the curare action of this on mice and frogs, pointing out that, in contrast to curare, it was also effective orally.⁶ Merck provided ampoules of curare and erythroidine for M. Burman at the Hospital for Joint Diseases in New York the following year, enabling him to compare the two drugs intravenously for treatment of patients with spastic and dystonic conditions. He concluded that, to produce muscle relaxation, erythroidine needed to be given in higher dosage compared to curare but had the advantage of being easier to acquire,

E-mail address: amckenzi@staffmail.ed.ac.uk.



Fig. 1. Klaus R.W. Unna (1908–1987): pharmacologist at the Merck Institute for Therapeutic Research, Rahway, NJ, until 1944; Professor at University of Illinois in Chicago 1955–1976 (Credit with permission: 064-01.unna.k.r.w.1., University of Illinois at Chicago Archives).

make up, and accurately assay. He presented his findings to the Boston Society of Psychiatry and Neurology in October 1938. In the discussion, A. Rosenbleuth asked whether Burman had ever given curare to a normal person, to which the answer was “not yet ... for no one has been willing to submit himself as a patient.”⁷ Burman is more widely remembered as the pioneer of arthroscopy.⁸

Folkers and colleagues further investigated erythroidine and, by 1939, found that it was a mixture of at least two isomers – α and β ; the β form was easier to purify.⁹ Pharmacologist K.R.W. Unna (Figure 1) confirmed that β -erythroidine had a curare-like action.¹⁰ Then Merck provided β -erythroidine in 1940 for Albany Hospital, New York, where S.R. Rosen and colleagues used it successfully by intravenous injection (although effective orally) prior to pentamethylenetetrazol-induced convulsions to prevent fractures in 37 patients. If respiratory depression occurred postseizure, this was readily reversed by neostigmine. The authors noted that the extremely variable potency of curare at that time rendered erythroidine the drug of choice. This publication was in the September 1940 issue of *Psychiatric Quarterly*.¹¹

Rosen had clearly not had access to the new Intocostrin preparation of curare produced by E.R. Squibb & Sons through the efforts of R. Gill. This product was standardized through the work of A.R. McIntyre, Professor of Pharmacology at the University of Nebraska, and H.A. Holaday, Chief of the Biological Assay Division of Squibb's Biological Laboratories; it was presented in ampoules of solution containing 20 U (1 U equated to 1 mg of “arbitrary curare standard preparation”) per milliliter.¹² One who did have access to Intocostrin was a psychiatrist at Bishop Clarkson Memorial Hospital in Omaha, NE, A.E. Bennett, who in January 1940 reported favorably on its use to prevent fractures from Metrazol-induced convulsive shock therapy.¹³ This was published in the widely read *JAMA*, so that Squibb now had a marketable drug.

However, a further clinical trial of β -erythroidine (intravenous) in pentamethylene-tetrazol (Metrazol) shock* was presented in November 1941 at the Illinois Psychiatric Society by W.R. Miller of Iowa City—he made no mention of Intocostrin. Satisfactory prevention of fractures was achieved in 47 patients given a total of 251 treat-

ments; artificial respiration was required on three occasions, and there was one case of sensitivity to the drug.¹⁴

In the same month, A.M. Harvey and R.L. Masland at the Institute of Neurology, University of Pennsylvania, published a more scientific comparison of “unauthenticated” curare (Squibb), β -erythroidine (Merck), and quinine methochloride. Studying 35 injections given to 23 patients, they used the electromyogram to estimate the degree of curarization. This was induced to the point at which the greatest action potential obtainable in response to a single supramaximal nerve stimulus was 40% of that prior to administration of the drug. They found that, with both β -erythroidine and quinine methochloride, the curarization was ephemeral (fairly rapid injection required to achieve full effect and return of full strength by about 10 minutes). With “unauthenticated” curare, the onset was slower but duration longer, with symptoms lasting up to 20 minutes. Whereas the “unauthenticated” curare produced no central effect, both quinine methochloride and β -erythroidine frequently caused drowsiness. For reducing the severity of pentamethylenetetrazol convulsions, they found the curare extract much more satisfactory than the other two drugs. In one patient (70 kg), a dose of 1.5 g of β -erythroidine over 2.5 minutes achieved curarization—he could not raise his head or legs—yet the pentamethylenetetrazol convulsions were severe.¹⁵

Following the suggestion of L. Wright (Squibb), on 23 January 1942, H.R. Griffith and G.E. Johnson at the Homeopathic Hospital, Montreal, used Intocostrin to deliberately give relaxation during surgery under cyclopropane anesthesia—in July, they published 25 cases of such use in *Anesthesiology*.¹⁶

In Liverpool (UK), anesthetists T.C. Gray and J. Halton heard about Intocostrin and managed to (unofficially) get some for anesthesia in thoracic surgery. They were disappointed by its lack of reliability and potency; furthermore, it was difficult to obtain during World War II. Therefore, in 1944, they used vials of d-tubocurarine powder (obtained from their physiology laboratory) with good effect.¹⁷

A problem with β -erythroidine was its short duration of action. Further work at Merck resulted in the preparation of dihydro- β -erythroidine (DH β E) in crystalline form. In 1943, K.R.W. Unna and colleagues reported that DH β E was equipotent with curarine (six times more potent than β -erythroidine), of acceptable duration, and also effective orally.¹⁸ Within weeks, the first clinical use of DH β E took place—in the treatment of tetanus. E.G. Goodman and J.F. Reinhardt of Duke University School of Medicine, Durham, NC, reported

* In the 1930s to 1940s, insulin-induced hypoglycemia or convulsant drugs such as pentamethylene-tetrazol (Metrazol, Leptazol) were used as convulsive shock therapy for depressive and schizophrenic states. This was gradually replaced in the late 1940s by electroconvulsive therapy.

how oral DH β E given hourly and then 2-hourly was a useful adjunct to treatment of a woman of 37 with postabortal tetanus—it successfully relaxed the neck muscles.¹⁹

It was the work of K.R.W. Unna that set the stage for DH β E to be used in general anesthesia. This was considered worthwhile for two reasons: (1) as crystalline, it could be accurately presented in mg/mL which was preferable to units according to bioassay, and (2) lack of histamine release. A problem with both Intocostrin and d-tubocurarine was histamine release from body tissues, sometimes producing bronchospasm. In 1946, J. Comroe and R.D. Dripps in Philadelphia investigated the effect of intracutaneous and intra-arterial injections of these and DH β E in 13 humans. They found that Intocostrin and d-tubocurarine produced huge weals and flares, whereas with DH β E this effect was minimal.²⁰

At the same unit, later in 1946, intravenous DH β E was trialed in clinical anesthesia on 215 patients by R.D. Dripps and W.F. Sargent. Recommending an initial dose of 50–75 mg, they concluded that the muscle relaxation it produced was indistinguishable from that of curare; hypotension (average fall in systolic blood pressure = 24 mm Hg, usually transient) occurred in 86% of patients—the main disadvantage; this was apparently a central effect. But an advantage was the lack of histamine release seen with curare derivatives.²¹ However, the publication of this paper (1947, also in *Anesthesiology*) was about 5 years after that on Intocostrin. Curiously, in 1946–1947, d-tubocurarine was noted to usually cause a rise in blood pressure,²² whereas by the 1970s, anesthetists were informed that it had the opposite effect: hypotension.²³ Perhaps, this could be explained by a change in pharmaceutical formulation.

By 1947, anesthetic use of Intocostrin in Canada¹⁶ and d-tubocurarine (produced by Burroughs Wellcome) in the United Kingdom²⁴ was becoming common. Merck did not “run with” DH β E and it was never made available commercially. But interest in oral DH β E for other uses prevailed for a while. In 1950, S. Shapiro and A.B. Baker at the University of Minnesota Medical School, Minneapolis, MN, reported that oral DH β E 200 mg daily improved rigidity in Parkinson disease (used as an adjunct to atropine derivatives).²⁵ Then, in 1951, W.D. Paul and D.C. Zavala described using oral DH β E 60 mg 6- to 8-hourly (20 mg in children) as a useful adjunct to overcome muscle spasm in poliomyelitis—with results comparable to curare.²⁶

The basic chemical structure of the erythrinane alkaloids was determined in 1951 by V. Prelog²⁷: nitrogen base tertiary rather than the quaternary arrangement in the curare alkaloids. This confers lipid solubility and the ability to penetrate the blood-brain barrier. The molecule of erythroidine includes a γ -aminobutyric acid-like moiety, perhaps responsible for sedation. Thus, the structure-activity relationships of the erythroidines are very different to those of other neuromuscular-blocking agents: besides blockade of the acetylcholine-activated ion channel, there is also (perhaps mainly) blockade of the cholinergic synapse between the recurrent collaterals of the lower motor neurones and the Renshaw cells in the spinal cord.²⁸

Conclusions

In 1947, erythroidines were potentially contenders with the early preparations of curare used in anesthesia. If the original publication on erythroidine had been in a more widely read journal, development of the erythroidines could have started earlier, with more

widespread use in anesthesia, instead of curare. From the late 1940s, more neuromuscular blockers were introduced into anesthetic practice, each addition making a return to the erythroidine derivatives more unlikely. This is another example of the influence of “timing and circumstance.”

Declaration

A version of this article was presented at the Ninth International Symposium on the History of Anesthesia, Boston, MA, October 2017.

References

1. del Pozo EC. Aztec pharmacology. *Annu Rev Pharmacol* 1966;6:9-18.
2. Dominguez M, Altamirano F. Del Colorin. *Gac Med Mex* 1877;12:77-91.
3. Remington JP, Wood HC, eds. *The Dispensary of the United States of America*; 1918. [<http://www.ibiblio.org/herbmed/eclectic/usdisp/erythrina.html>, accessed 29/02/2004].
4. Lehman AJ. Actions of *Erythrina americana*, a possible curare substitute. *J Pharmacol Exp Ther* 1937;60:69-81.
5. Ramirez E, Rivero MD. Contribucion al estudio de la accion farmaco-dinamica de la *Erythrina Americana*. *Ann Inst Biol (Mex)* 1935;6:301-305.
6. Folkers K, Major RT. Isolation of erythroidine, an alkaloid of curare action, from *Erythrina americana* Mill. *J Am Chem Soc* 1937;59:1580-1581.
7. Burman MS. Therapeutic use of curare and erythroidine hydrochloride for spastic and dystonic states. *Arch Neurol Psychiatry* 1939;41:307-327.
8. Parisien JS, Michael S. Burman, the pioneer: a tribute. In: Parisien JS, ed. *Arthroscopic Surgery*. New York: McGraw-Hill Inc.; 1988:xiii.
9. Folkers K, Koniuszy F. *Abstracts of Papers, 97th Meeting of the American Chemical Society, Baltimore, MD, April 1939*. Division of Organic Chemistry; 1939:17.
10. Unna K. Curare-like action of *Erythrina* alkaloids. *Am J Physiol* 1939;126:644-645.
11. Rosen SR, Cameron DE, Ziegler JB. The prevention of metrazol fractures by beta-erythroidine hydrochloride. *Psychiatr Q* 1940;14:477-480.
12. Squibb E.R. & Sons. *Curare Intocostrin*. New York: ERSquibb & Sons; 1946:42. [144, 170].
13. Bennett AE. Preventing traumatic complications in convulsive shock therapy by curare. *JAMA* 1940;114:322-324.
14. Miller WR. Clinical experience with beta erythroidine hydrochloride in metrazol shock. *Arch Neurol Psychiatry (Proc)* 1942;47:508-510.
15. Harvey AM, Masland RL. Actions of curarizing preparations in the human. *J Pharmacol Exp Ther* 1941;73:304-311.
16. Griffith HR, Johnson GE. The use of curare in general anaesthesia. *Anesthesiology* 1942;3:418-420.
17. Gray TC. Luck was a lady. In: Atkinson RS, Boulton TB, eds. *The History of Anaesthesia*. London: RSM Services Ltd.; 1989:16-19.
18. Unna KRW, Kniazuk M, Greslin JG. Pharmacologic action of erythrina alkaloids I. β -erythroidine and substances derived from it. *J Pharmacol Exp Ther* 1944;80:39-52.
19. Goodman EG, Reinhardt JF. Postabortal tetanus: successful treatment with dihydro-beta-erythroidine. *South Med J* 1943;36:737-738.
20. Comroe JH, Dripps RD. The histamine-like action of curare and tubocurarine injected intracutaneously and intra-arterially in man. *Anesthesiology* 1946;7:260-262.
21. Dripps RD, Sargent WF. Use of a new curarizing agent: dihydro-beta-erythroidine, for the production of muscular relaxation during anesthesia and surgery. *Anesthesiology* 1947;8:241-251.
22. Prescott F, Organe G, Rowbotham S. Tubocurarine chloride as an adjunct to anaesthesia. *Lancet* 1946;ii:80-84.
23. Coleman AJ, Downing JW, Leary WP, Moyes DG, Styles M. The immediate cardiovascular effects of pancuronium, alcuronium and tubocurarine in man. *Anaesthesia* 1972;27:415-422.
24. Gray TC, Halton JA. A milestone in anaesthesia? (d-tubocurarine chloride). *Proc R Soc Med* 1946;39:400-410.
25. Shapiro S, Baker AB. Treatment of paralysis agitans with dihydro-beta-erythroidine. *Am J Med* 1950;8:153-159.
26. Paul WD, Zavala DC. Management of spasm in poliomyelitis. *Med Times* 1951;79:463-467.
27. Kenner GW, Khorana HG, Prelog V. Erythrina-Alkaloide 3. Mitt. Über den Hofmann'schen des Tetrahydro-erysotrin und des Tetrahydro-erythralins. *Helv Chim Acta* 1951;34:1969.
28. Bowman WC. *Pharmacology of Neuromuscular Function* 2nd ed.; 1990:139-140.