

## PHARMACOLOGICAL STUDIES ON NOVEL BASIC AMINOALKYL ARYL ETHERS AS POTENTIAL LOCAL ANAESTHETICS

D. AL-SAAD, \* M.Sc., Ph.D., AND W.E. SNEADER, \*\* Ph.D.

From the \*School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran, and \*\*School of Pharmacy and Pharmacology, University of Strathclyde, Glasgow, Scotland.

### ABSTRACT

Following our previous investigations on certain new aminoalkyl aryl ethers, which showed promising and outstanding local anaesthetic properties, the local anaesthetic activity and duration of action of a further selection of four novel derivatives of the above-mentioned series, used as hydrochloride salts, have been determined by the *in vivo* rat sciatic nerve test. These are: *N,N*-dimethyl-2-(2,6-di-*tert*-butylphenoxy)ethylamine; *N,N*-dimethyl-2-(4-butoxyphenoxy)ethylamine; *N,N*-dimethyl-2-(2,6-di-*sec*-butylphenoxy)ethylamine; and *N,N*-diethyl-2-(4-*sec*-butylphenoxy)ethylamine. The tests have been performed by a double blind, controlled trial (at the later stage) and in two stages. Bupivacaine hydrochloride has been employed as the standard and normal saline as the control. The complete loss of motor function of the injected limb of the animal is considered as a positive response, which is assessed by observing the animal gait and ability to climb up a sloping wire mesh. The test compounds have exhibited shorter duration of motor paralysis than that of the standard and comparable rates of both onset of action, and recovery time from full analgesia. They also have shown neither apparent systemic nor local side effects such as edema, swelling, induration, ulceration, necrosis, or irritation. *MJIRI, Vol. 7, No. 3, 187-191, 1993.*

**Keywords:** Anaesthetics, local; basic aminoalkyl aryl ethers, pharmacology; rat sciatic nerve block, new local anaesthetics; bupivacaine, *in vivo* studies.

### INTRODUCTION

Although many reliable local anaesthetics are available, anaesthetists who use nerve blocks for pain relief and other therapeutic purposes would welcome a non-necrotizing local anaesthetic compound or preparation, which would

provide a block lasting days or weeks.<sup>1,2</sup> The characteristics of such a product include: complete reversibility of action, freedom from local and systemic side effects, high potency, reasonably rapid onset of action, complete and quick recovery from anaesthesia, effectiveness topically as well as by injection, minimal systemic toxicity and high therapeutic index, ready metabolism and excretion, stability during storage and sterilization, high reproducibility, and an appropriate solubility that permits chemical assay.<sup>3,5</sup> Unfortunately, so far no safe drug or preparation has come into clinical use to control prolonged and severe pain. Therefore, attention was focused on aminoalkyl aryl ethers as potential long-acting local anaesthetics for various

Correspondent author:

D. Al-Saadi, M.Sc., Ph.D.

Associate Professor,

Head, Department of Pharmaceutical Chemistry, School of Pharmacy,

Mashhad University of Medical Sciences, P.O. Box 91775-1365,

Mashhad, Iran

## Aminoalkyl Aryl Ethers as Local Anaesthetics

reasons. Firstly, there are several reports in the literature of a prolonged action arising from a variety of aminoalkyl ether local anaesthetics.<sup>6,7</sup> Secondly, both the ester and amide (anilide) series have been extensively investigated in a fairly systematic manner.<sup>8,9</sup> Thirdly, the salts of these ethers are all water soluble at the concentration required to produce anaesthesia. The final factor which supported investigation of a series of basic aminoalkyl aryl ethers was the recognition of the wide diversity of such compounds reported in the literature to exhibit local anaesthetic action, yet no systematic detailed study of such compounds have been reported.

Thus a large series of basic aminoalkyl aryl ethers (*N*, *N*-dialkyl (mono-, di-, trisubstituted phenoxyethylamines) were prepared<sup>3</sup> and assessed as potential long-acting local anaesthetics. These compounds displayed, in the guinea pig intradermal wheal test, excellent profiles of anaesthesia and were as good as or better than both of the standard agents (lidocaine and bupivacaine) in terms of onset and duration of action, time of recovery, and lack of untoward side effects.<sup>3</sup> Moreover, the promising and interesting results of our previous investigations<sup>2</sup> on certain derivatives of the above-mentioned series have encouraged us to perform additional pharmacological studies to confirm their intensity and duration of action.

Accordingly, based on the results of both the guinea pig intradermal wheal test (WT) and the rat sciatic nerve block (RSNB),<sup>2,3</sup> four new compounds of the aforementioned series<sup>3</sup> were chosen (Fig. 1) for further studies on the rat sciatic nerve preparation *in vivo*. The potency and duration of action were determined by a double blind, controlled test (at the later stage), and in two stages. The results of this investigation are reported in this communication.

### MATERIALS AND METHODS

**1-Materials:** Male or female rats of approximately 200-250 gm weight were used. Solutions of the test agents (*N*, *N*-dimethyl-2-(2,6-di-*tert*-butylphenoxy)ethylamine (1A); *N*, *N*-dimethyl-2-(4-butoxyphenoxy)ethylamine (2A); *N*, *N*-dimethyl-2-(2,6-di-*sec*-butylphenoxy)ethylamine (3A); and *N*, *N*-diethyl-2-(4-*sec*-butylphenoxy)ethylamine (4A), in the form of HCl-salts,<sup>3</sup> 0.5 or 1% W/V in 0.9% W/V normal saline, were freshly prepared. A small tuberculin syringe and a 26 gauge needle were employed for injection. A sloping wire mesh at an angle of 30 degrees to the horizontal was used for assessing the duration of motor anaesthesia.

**2-Method:** Triplicate sets of three or duplicate sets of six groups of two male or female rats were used. Each rat received 0.2 ml injection of the anaesthetic solution into the posterior aspect of the femur head. A positive effect

**Table I. Results of duration of action of compound 1A (min), using 9 male and female rats**

Expt. no.	1A(%)	Bupivacaine (0.5%)	Saline (0.9%)
1	100	180	0
2	120	120	0
3	82	240	0
4	90	165	0
5	0	160	0
6	180	180	0
7	0	180	0
8	60	180	0
9	0	180	0
Mean of 9	70.22	176.11	
S.D.	62.09	3100	
S.E.	20.70	10.33	
Sample size	9	9	
Mann Whitney U-Test results			
T max.	126.00	--	--
T min	45.00	--	--
T	51.00	--	--
U	6.00	--	--
R2	120.00	--	--
P	≤0.05	--	--
Results	Signif.	--	--
t-Test results			
t	3.39	--	--
P	≤0.05	--	--
Result	Signif.	--	--

was shown by a complete loss of motor control of that limb. This was determined by observing the animal movement and ability to climb up the sloping wire mesh. The duration of local anaesthesia was gauged by the duration of full motor paralysis to the first sign of motor sensation. Animals were observed at 5 min intervals for the first 30 min, at 10 min intervals over the following 2 h period, at 30 min intervals for up to 10 h, and thereafter at 6-10 h intervals.<sup>2</sup>

### RESULTS

The results are shown in Tables I, II, and III.

### DISCUSSION

An appreciable anaesthetic response was observed during the preliminary stage which represented the pilot study. It required six animals and served to establish the approximate duration of motor anaesthesia as well as demonstrating any

Table II. Results of duration of action of compounds 1A, 2A, 3A, and 4A (min), at 0.5% W/V concentration, using 12 male and female rats

Expt. no.	1A	2A	3A	4A	Bupivacaine	Saline (0.9%)
1	0	1800	10080	120	120	0
2	10080	0	1800	330	270	0
3	10080	1440	10080	0	1440	0
4	240	120	120	10080	240	0
5	240	0	80	240	240	0
6	60	0	420	420	420	0
7	330	0	0	480	360	0
8	50	360	180	90	360	0
9	60	60	0	0	300	0
10	0	0	0	240	240	0
11	210	0	210	180	210	0
12	0	210	105	150	210	0
Mean of 12	≅1780	≅315	≅1925	≅1028	≅370	--
S.D.	≅3880	≅625	≅3840	≅2855	≅350	--
S.E.	≅1120	≅180	≅1110	≅824	≅100	--

defects and/or errors in the experimental system as a whole. Based upon the positive findings of this stage, the study continued to the second stage on a double blind, controlled trial. It required nine or 12 animals, where the precise duration of motor paralysis was determined. As shown in Table I, the mean duration of action of compound 1A at 1% W/V concentration was  $70.22 \pm 62.09$  min, while that of the bupivacaine standard was  $176.11 \pm 31.00$  min. Statistical analysis by the Mann-Whitney U test<sup>10,11</sup> indicated that, at 5% significance level (probability  $\leq 0.05$ ), the difference in duration of action between this compound and the control (placebo) is very highly significant. This refers that there is a genuine local anaesthetic activity and also the apparent difference between the duration of action of compound 1A and the standard agent is real and not accidental. Comparable results were obtained by the t-test analysis (Table I). However, the Mann-Whitney U test was preferred on theoretical grounds. Moreover, statistical analysis demonstrated that the nine rats had not been enough to obtain a concrete conclusion. Thus, more animals are required to draw a more reliable answer regarding the duration of action of this compound in comparison to the standard agent.

Therefore, the results obtained, so far, from this and previous studies<sup>2</sup> have warranted investigating other derivatives of the above-mentioned series, but at 0.5% W/V concentration, i.e. compounds 2A, 3A and 4A together with compound 1A. In the second set of experiments 12 male and female rats were used. These compounds as well as the standard agent all have also exhibited a widely variable duration of motor anaesthesia (Table II). Once more, the standard deviations were large in relation to the values of means, indicating that results obtained from

testing the compound on 12 male and female rats had not been adequate for statistical validity. Thus, as in the previous situation, more assays are required to obtain a valid answer concerning the duration of anaesthesia of these agents in comparison to the standard.

Many factors have been found to affect drug metabolism,<sup>12,19</sup> and generally, sex-dependent variation in drug metabolism has been well documented in rats but not in other rodents. It has been reported that young adult male rats metabolize several drugs at a much faster rate than mature female rats or prepubertal male rats. These differences are also dependent on substrate, because some xenobiotics are metabolized at the same rate in both female and male rats.<sup>14,15</sup> Therefore, it is most probable that the wide variation in the duration of motor anaesthesia of the test compounds and the standard agent could be due to sex differences in drug biotransformation, which, in turn, is strongly dependent on the nature of the substance, and/or to individual variations, i.e. the aminoalkyl aryl ether type test agents are metabolized in a different pathway as well as at a faster rate than that of the bupivacaine standard anilide type local anaesthetic. At any rate, additional studies are required to confirm these conclusions.

Accordingly, these compounds have been assayed further on only 12 male rats (Table III). They have produced more reproducible results and the difference in the duration of action among them has been significantly less than that observed in the previous sets of experiments. This gives an additional support to our aforementioned conclusions concerning the importance of sex differences as well as the chemical nature of the substrate and their profound influence on the duration of motor anaesthesia of these compounds. The results reported by other workers are in agreement

## Aminoalkyl Aryl Ethers as Local Anaesthetics

**Table III. Results of duration of action of compounds 1A, 2A, 3A and 4A (min), at 0.5% W/V concentration, using only male rats**

Expt. no.	1A	2A	3A	4A	Bupivacaine	Saline (0.9%)
1	90	120	80	180	120	0
2	80	120	80	180	180	0
3	100	90	100	150	270	0
4	100	60	0	120	150	0
5	60	0	60	120	150	0
6	120	80	240	0	150	0
7	60	210	60	0	360	0
8	100	70	180	0	180	0
9	80	60	0	150	120	0
10	0	90	110	150	240	0
11	120	0	120	240	360	0
12	60	110	70	0	180	0
Mean of 12	≅81	≅84	≅92	≅95	≅205	
S.D.	≅33	≅56	≅67.8	≅89.4	≅84.7	
S.E.	≅9.6	≅16	≅19.7	≅25.8	≅24.4	
t-Test results						
t	0.22	0.46	1.05	3.2		
P	≤0.05	≤0.05	≤0.05	≤0.05		
Result	Signif.	Signif.	Signif.	Signif.		

with our findings.<sup>12,18</sup>

In addition, the duration of action of the standard agent generally is longer than that of test compounds. This may also be attributed to the vasoconstrictive effect of the standard, leading to decreasing its rate of absorption into systemic circulation and in turn, delaying the rate of the standard agent metabolism. The vasoconstrictive property of the bupivacaine standard is obviously less effective in areas which are sparsely perfused with blood capillaries. This is well noticed with the results of the wheel test,<sup>3</sup> where these compounds displayed longer duration of full, reversible local anaesthesia (≥24 h) than that of the standard agent (2 h). Conduction velocity and duration of anaesthesia have been reported to be related to fibre diameter.<sup>2</sup> Thus, the apparent difference between duration of anaesthesia of these compounds using WT and RSNB can be explained on the basis of variation of the nerve size. The former anaesthetizes sensory nerves, which have small diameter; while the latter blocks motor nerve fibres of larger size.

In conclusion, since the action of the test agents is

reversible, no apparent unwanted local side effects have been observed, and good anaesthetic properties are displayed, i.e. quick onset of action and short, complete recovery from anaesthesia, we feel that these criteria, collectively, justify carrying out additional pharmacological studies on other types of animals and also other kinds of nerve block tests as well as further toxicological investigations on these and other derivatives of the above-mentioned series in order to verify these conclusions and to determine their ultimate mechanism of action, safety and effectiveness before taking any clinical decision and also to select the outstanding compounds of this class of local anaesthetics. Also, they may represent new, potential candidates for the relief of chronic and severe intractable pain associated with uncountable clinical and pathological cases.

### ACKNOWLEDGEMENTS

We thank Drs. A. Burke, A. Gillies, and W. Sniper, Department of Anaesthesia, Victoria Infirmary, Glasgow,

Scotland, for their cooperation in this project. Thanks are also due to Mrs. E. M. Fakhr for her invaluable help in preparing the manuscript.

### REFERENCES

1. Adriani J: The clinical pharmacology of local anaesthetics. *Clin Pharmacol Ther* 1: 645-73, 1960.
2. Al-Saadi D, Sneader WE: Pharmacological evaluation of certain novel prolonged-acting local anaesthetics. *Arzneim-Forsch/Drug Res* 41: 195-8, 1991.
3. Al-Saadi D: Potential Long-Acting Local Anaesthetics, Ph.D. Thesis, School of Pharmacy, University of Strathclyde, Glasgow, Scotland, 1981.
4. Dripps RD, Eckenhoff JE, Vandam LD: Introduction to Anesthesia. Philadelphia: W.B. Saunders Company, 211-22, 1988.
5. Concepcion M, Covino BG: Criteria for selecting the best local anesthetic agent. *Curr Rev Clin Aesth* 20: 155-63, 1986.
6. Kashkina NA, Pormale M, Lauberte H, Kalnins A, Susters J, Mikazans V, Purvins I, Skutelis A: Polymeric forms of 2-dimethylaminoethyl  $\rho$ -(butylamino) benzoate. USSR Pat 621648, 1978; Chem Abst 89: P204-227b, 1978.
7. Weiner BZ, Zilkha A: Polyethylene glycol derivatives of procaine. *J Med Chem* 16: 573-6, 1973.
8. Büchi J, Perlia X: The design of local anesthetics. In: Ariëns EJ (ed). *Drug Design*, Vol III, New York: Academic Press, 243-391, 1972.
9. Büchi J, Perlia X: Structure-activity relations and physico-chemical properties of local anesthetics. In: Lechat P(ed). *Int Pharmacol Ther*, Vol I, Sec 8, Oxford: Pergamon, 39-129, 1971.
10. Siegel S: *Non-Parametric Statistics for Behaviour Sciences*. New York: McGraw Hill, 116-26, 1956.
11. Armitage P: *Statistical Methods in Medical Research*, Oxford: Blackwell Scientific Publications. 269-301, 1971.
12. Testa B, Jenner P(ed.): *Drug Metabolism: Chemical and Biochemical Aspects*. New York: Marcel Dekker, 329-418, 1976.
13. Goth A: *Medical Pharmacology: Principles and Concepts*. St. Louis, C.V. Mosby, 29-39, 1984.
14. Low LK, Castagnoli N Jr: Metabolic changes of drugs and related organic compounds. In: Delgado JN, Remers WA (ed.): *Textbook of Organic Medicinal and Pharmaceutical Chemistry*. Philadelphia: J.B. Lippincott, 45-127, 1991.
15. Correia MA, Castagnoli N Jr: Pharmacokinetics. II. Drug biotransformation. In: Katzung BG (ed.): *Basic and Clinical Pharmacology*. Norwalk: Appleton & Lange, 36-43, 1987.
16. La Du BN, Mandel HG, Way EL: *Fundamentals of Drug Metabolism and Drug Disposition*. Baltimore: Williams & Wilkins, 1971.
17. Schreiber EC: The metabolic alteration of drug. *Ann Rev Pharmacol* 10: 77, 1970.
18. Nelson SD: Chemical and biological factors influencing drug biotransformation. In: Wolff ME (ed). *Burger's Medicinal Chemistry*. Part 1, New York: Wiley-Interscience, 227-69, 1980.
19. Low LK, Castagnoli N: Drug biotransformations. In: Wolff ME (ed.). *Burger's Medicinal Chemistry*. Part 1. New York: Wiley-Interscience, 107-226, 1980.
20. Mitchell JR, Horning MG (eds.): *Drug Metabolism and Drug Toxicity*. New York: Raven Press, 1984.