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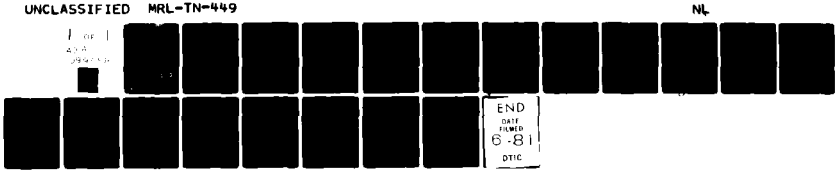

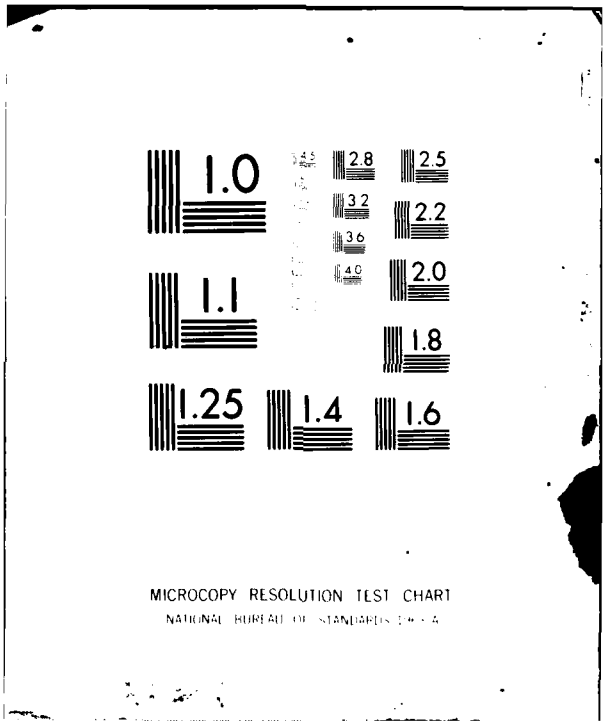
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MRL-TN-449

AN EXAMINATION OF THE FEASIBILITY OF ADMINISTERING PROPHYLACTIC PYRIDOSTIGMINE BY THE PERCUTANEOUS ROUTE

Hugh D. Crone and Michael P. Bladen

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The feasibility of administering pyridostigmine by the percutaneous route was examined by the use of guinea pigs *in vivo* and their skin *in vitro*. Pyridostigmine has a possible use as a prophylactic against poisoning by organophosphorus esters. The compound enters the animal to inhibit blood cholinesterase, producing effects observable in 30 minutes. Evidence of the storage of pyridostigmine in skin was found. The compound when crossing skin *in vitro* takes 1,000 minutes to reach an equilibrium rate. A permeability constant of 2×10^{-6} cm min^{-1} was estimated. The main problem remaining is the practical one of making a dosage form suitable for presenting the pyridostigmine at constant concentration to the skin for a long period.

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16. *ABSTRACT (if this is security classified, the announcement of this report will be similarly classified):*

The feasibility of administering pyridostigmine by the percutaneous route was examined by the use of guinea pigs *in vivo* and their skin *in vitro*. Pyridostigmine has a possible use as a prophylactic against poisoning by organophosphorus esters. The compound enters the animal to inhibit blood cholinesterase, producing effects observable in 30 minutes. Evidence of the storage of pyridostigmine in skin was found. The compound when crossing skin *in vitro* takes 1,000 minutes to reach an equilibrium rate. A permeability constant of 2×10^{-6} cm min^{-1} was estimated. The main problem remaining is the practical one of making a dosage form suitable for presenting the pyridostigmine at constant concentration to the skin for a long period.

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AN EXAMINATION OF THE FEASIBILITY OF ADMINISTERING PROPHYLACTIC PYRIDOSTIGMINE BY THE PERCUTANEOUS ROUTE

1. INTRODUCTION

There is current interest in the administration of drugs by the percutaneous route as opposed to oral dosing. Thus Alza Corporation has recently introduced a device [1] which administers scopolamine through the skin for the control of motion sickness, and a glyceryl trinitrate ointment and applicator [2] is available for the prevention of angina pectoris, as an alternative to tablets for sublingual administration. Weakly basic or acidic drugs are most suitable for percutaneous administration, as they can be presented to the skin in neutral form for rapid absorption. This would make atropine and related anticholinergics the obvious candidates among the drugs currently used for the treatment of organophosphorus poisoning. On the other hand, the benefits of such a dosage route would be mainly in prophylaxis, as the percutaneous route would be too slow for therapy. This turns attention to pyridostigmine, which is a candidate prophylactic drug but also a strongly basic compound. It was thought worthwhile to examine the skin uptake of pyridostigmine to assess the usefulness of this route. The expected benefit is the maintenance of a constant pyridostigmine concentration in the blood over a long period of time, as opposed to the fluctuations arising from oral dosage [3].

This report describes the initial stages of this feasibility study, in which the movement of pyridostigmine across the skin of the guinea pig was examined *in vivo*, and mounted in a skin permeation cell. Since we did not have a sufficiently sensitive chemical assay for the drug, we measured the inhibition of acetylcholinesterase (AChE) as an indirect assay. Experiments were also done with ^{14}C-labelled pyridostigmine.

The research described here is in support of a programme seeking new methods of prophylaxis and therapy for poisoning by nerve agents. This is part of the MRL task, Defence Against Chemical Agents, and also forms an Australian contribution to the programme of TTCP Subgroup E, Technical Panel 1.

2. METHODS

Adult female guinea pigs were shaved on the back, then inspected for macroscopic skin damage. Pyridostigmine bromide in various forms was applied to the skin over a defined area and covered with a rubber membrane. For the experiments reported in Fig. 1, the aqueous drug solution was thickened with 10 mg mL^{-1} of SGP powder (Water Soluble Polymer, Henkel Australia Ltd) and 0.01 per cent w/v Triton X-100. At known time intervals after drug application, blood samples were obtained by nicking the ear of the animal, and whole blood cholinesterase activity was assayed by the Ellman thiocholine technique [4].

The infusion experiments were performed on guinea pigs under urethane anaesthesia. Known concentrations of pyridostigmine in isotonic saline were infused at 5.9 $mL.h^{-1}$ into the jugular vein, and samples of blood for assay were collected when required from a cannula in the carotid artery.

The skin permeation cell was of a standard type similar to that illustrated by Tregear [5]. The diameter of the cell body and thus of the effective skin area was 10 mm and the depth of the inner cell was 3.5 mm. The fluid in the inner cell was stirred magnetically with a 5 mm length of stainless steel wire, 0.55 mm diameter. The cell was maintained at 37°, and a buffer solution of 150 mM NaCl, 5 mM Tris-HCl, pH 7.4 (37°) was circulated through the stirred inner cell at 4.5 $mL.h^{-1}$. Full-thickness guinea pig skin was clamped in the cell. To measure the inflow of pyridostgmine, 160 µg mL^{-1} of Sigma bovine erythrocyte acetylcholinesterase (AChE) was added to the buffer solution. After a settling down period of 80 or 120 min, the effluent AChE activity was found to equal that of the stock reservoir. Then the test sample of the pyridostigmine solution was applied to the epidermal side of the skin, and te internal circulating buffer was collected in 3 mL fractions (40 min) for AChE assay. The permeation by radioactive pyridostigmine was performed in an identical manner; the effluent was then monitored by standard scintillation counting techniques. An aqueous sample of 0.5 mL was added to 10 mL of a mixture of 40 mg PPO, 0.6 g naphthalene, 9 mL dioxan and 1 mL methanol.

3. RESULTS

3.1 Whole Animal Uptake Studies

Pyridostigmine entered the bloodstream and inhibited ChE within 30 min when applied to the shaven skin of the guinea pig (Fig. 1). After 2 to 3 hours the level of inhibition reached a constant value, implying that pyridostigmine entry had come to a steady state. The constant level of ChE inhibition was related to the dose of drug applied. The experiments illustrated in Fig. 1 were extended beyond the time shown, in one case to 6 days. The pad of pyridostigmine was removed after 22 h in this experiment, but inhibition of ChE was observed at 4 days after the initial dosing, and the other experiments showed a recovery time greater than 3 days after removing the pyridostigmine pad and washing the skin. Immediately after this washing procedure in one experiment the ChE activity dropped from 66% to 41% of control, then gradually recovered.

An experiment was then performed to find whether the blood cholinesterase could be maintained partially inhibited for a number of days. A guinea pig was treated with a fresh pad of 100 mg/mL pyridostigmine gel on 2 cm^2 each day for 4 days. Cholinesterase activity was 74% of the starting value at 5 h, 49% at 25 h, then declined slowly to 20% at the fourth day. At this point the animal was showing symptoms of cholinesterase poisoning. The pad was removed and the skin washed. Recovery to 93% was observed after a further 3 days. Two experiments were performed in which moist, solid pyridostigmine was applied to the skin over areas of 0.5 cm^2 and 0.125 cm^2. Minimum cholinesterase activities of 55% (at 29 h) and 58% (at 24 h) respectively were observed. The main problem in all these experiments was to maintain the pads in position on the animal and prevent the gel from drying out. Because of these problems it was not possible to obtain good reproducibility in results.

These experiments showed that pyridostigmine can enter the blood stream by the percutaneous route within minutes of application, that a quasi-equilibrium in entry rate is reached in 2 to 3 hours and that an animal may be maintained with the blood cholinesterase partially inhibited for a period of days. The fact that recovery of the ChE requires several days after the pyridostigmine is washed from the outside implies that this recovery is not limited by the decarbamylation of the enzyme (half life 3 h for bovine erythrocyte AChE at 25° pH 7.0, ref. 6), but to the presence of a reservoir of pyridostigmine in the skin or another tissue.

The inhibition of blood ChE was then followed when solutions of pyridostigmine were infused at constant rate into the jugular vein of anaesthetised guinea pigs. The plots of inhibition versus time were very similar to those of Fig. 1, but since the experiments were terminated at 200 min, an apparent equilibrium level was not always established. It was possible to use the data from the infusion experiments to equate the degrees of inhibition observed in Fig. 1 with rates of percutaneous entry of pyridostigmine, and hence calculate an approximate permeability constant for the drug through the skin. The calculation is shown in Table 1 for the three experiments from Fig. 1 that could be reasonably interpolated in the infusion experiment results. Fick's law is obeyed as far as the limited data can show, and a reasonable estimate of the permeability constant is 2×10^{-6} cm min^{-1}.

3.2 Permeation Cell Experiments

Initially two sets of experiments were done in a similar manner to those performed on the whole animal, that is the AChE inhibition caused by diffusion across the skin was compared to that produced by direct infusion of pyridostigmine solutions into the cell. This was achieved by a needle inserted through the skin. Depression of AChE activity in the second fraction collected after drug application was observed when the topical pyridostigmine concentration was equal to or greater than 50 mg/mL. Effects in the first 40 min were sometimes seen when the external concentration was 200 or 400 mg/mL. The rate at which the AChE activity fell was approximately proportional to pyridostigmine concentration. In the 280 min for which these experiments were run, the AChE activity did not come to a steady state of inhibition, implying that the rate of entry of pyridostigmine was still increasing after this period. The results from different experiments were quite variable.

By direct injection at constant rate of known pyridostigmine solutions across the skin it was possible to relate the degree of inhibition of AChE in the effluent to the rate of entry of the inhibitor. The rate which gave 50% inhibition was 350 mg h^{-1}; taking into account the volume of buffer flowing through the cell, this is equal to 2.5×10^{-7} M.

A 50% inhibition at equilibrium was found to occur when between 20 and 50 mg/mL pyridostigmine was placed on the ouside of the skin. If we assume this value to be 40 mg/mL, resulting in an entry rate of 350 mg h^{-1}, then a permeability constant of 1.8×10^{-7} cm min^{-1} is obtained; a tenth of that calculated for the whole animal.

3.3 Movement of ^{14}C-labelled Pyridostigmine Across Skin in the Permeation Cell

When ^{14}C-labelled pyridostigmine (185 kBq, 0.62 µmoles, 162 µg, in 0.2 mL buffer diluted 1 + 1 with water) was applied to the outside of the skin, a detectable level of radioactivity appeared inside the cell within 40 min but a steady level was not reached for many hours. In one experiment a levelling was found after 1,000 min (Fig. 2), at 24.5 Bq mL^{-1}, which is equivalent to a permeability constant of 2.5×10^{-6} cm min^{-1}.

When the ^{14}C-pyridostigmine solution (I = 0.075) was washed from the outside of the skin and replaced with buffer solution (I = 0.153) it was noticed in several experiments that the level of radioactivity rose immediately on the inside before slowly falling below the original level (Fig. 2). It was thought that this could be due to the release of pyridostigmine stored in the skin by the change in ionic strength from dilute buffer to isotonic bufer. To test this, the experiment illustrated in Fig. 3 was performed. The ^{14}C-pyridostigmine was added in aqueous solution with no buffer salts present, left for 1320 min, washed off with the isotonic buffer several times, and buffer left in contact with the outer surface. A very marked rise in radioactivity leaving the inner surface of the skin was seen, and washout was not complete after a further 400 min. Of the 162 µg of pyridostigmine applied, 141 µg was recovered from the outside, 0.65 µg crossed to the inside during the application period and a further 1.6 µg during the wash period. There were 4.4 µg left in the skin after the experiment, giving a recovery of 147.65 µg (91 per cent). If we assume that during the wash period, equal quantities were washed out in each direction, then the skin held 7.6 µg of pyridostigmine (9.7 µg cm^{-2}).

These experiments show that a steady rate of entry is not achieved for at least 1000 min, that the skin holds a considerable store of pyridostigmine, and that changes in the environment of the outer surface of the skin can cause an immediate release of pyridostigmine from the inner surface. The effect of an increase in ionic strength of the wash solution suggests that the binding to the skin is ionic in nature.

3.4 Effect of the Solvent on Pyridostigmine Movement Through Isolated Skin

Pyridostigmine at 20 mg mL^{-1} in water did not pass through guinea pig skin *in vivo* over 240 min as judged by the failure to inhibit AChE (Fig. 4). This concentration of pyridostigmine was applied in various alcohols and other solvents to compare the effect of the vehicle on entry of the drug. Representative results are shown in Fig. 4. The solvents may be ranked in

increasing order of facilitating entry of the drug as: Water = Polyethylene glycol 200 < ethanol < n-butanol < n-propanol < n-heptanol < i-amyl alcohol. Another experiment was performed in which the outside of the skin was exposed to i-amyl alcohol for 160 min, which was then washed off with repeated changes of water over 40 min. Then 20 mg mL^{-1} of pyridostigmine in water was applied and the inhibition of AChE on the inner side was measured. This occurred at a rate nearly as fast as when the drug was dissolved in i-amyl alcohol, between that observed for n-propanol and n-heptanol.

The last experiment proves that the effect of the vehicle on pyridostigmine entry is related to a long-lasting effect on the skin structure, and not to a direct property of the drug in solution, such as an alteration in the partition coefficient between vehicle and stratum corneum [7]. This effect was probably due to the removal of lipid material from the stratum corneum, as described by Creasey *et. al.*[8]. However, it is difficult to see why n-propanol should have been more effective in this removal than n-butanol.

3.5 Examination of Means of Applying Pyridostigmine to Skin

The pyridostigmine was applied in the whole animal experiments as an aqueous solution gelled with a semi-synthetic polymer (SGP water soluble polymer: Henkel Australia Ltd.). This formed a soft gel, which was not adherent. What is required is a gelling agent which will also be tacky, and not dry out. The Alza Corporation device employs polyisobutylene mixed with mineral oil, in which the free base scopolamine will dissolve. Pyridostigmine obviously presents solubility problems in such a system. Experiments were made in which various mixtures of mineral oil and different alcohols were tried as solvents for pyridostigmine bromide, as the ion pair. The best result to date was obtained with a mixture of mineral oil, ethanol and n-butanol which contained 2 mg mL^{-1} of pyridostigmine bromide. If too much alcohol is added to the oil, then the polyisobutylene will not dissolve in the mixture. The problem of a vehicle for the pyridostigmine is continuing to be examined.

4. DISCUSSION

The *in vivo* and the longer term *in vitro* results suggest that the permeability constant for pyridostigmine through guinea pig skin is approximately 2×10^{-6} cm min^{-1}. The value of 1.8×10^{-7} cm min^{-1} obtained from the *in vitro* results with unlabelled pyridostigmine probably reflects a failure to achieve an equilibrium situation in the short time the experiments were run. The permeability constant is of the same order of magnitude as that found for undiluted organophosphorus esters and for a number of organic compounds in aqueous solution, passing through rabbit and human skin [5]. There is a significant reservoir for pyridostigmine in the skin; possibly the compound is bound to anionic polymers. These results do not allow appendageal diffusion (through hair follicles) to be differentiated from diffusion through the stratum corneum. However, it could well be that the entry observed in the short term (30 min) was due to the former, and that the equilibrium finally observed after 1000 min or more was due to the latter. In the long term

dosing situation, the properties of the stratum corneum would be the controlling factors.

The present study is not extensive enough to determine whether percutaneous dosage is a practical means of giving prophylatic pyridostigmine to humans. Further characterisation of the stratum corneum (especially in humans) is required, and also the examination of dosage forms. The technological problems of the latter may well decide the fate of this concept.

Nevertheless we feel that the idea is worthy of further effort, and intend to examine the concept again when resources permit.

5. CONCLUSION

1. The permeability constant of pyridostigmine through guinea pig skin is approximately 2×10^{-6} cm min^{-1}.

2. An equilibrium rate of penetration is attained in not less than 1000 min.

3. The epidermis acts as a store of pyridostigmine, which can be released rapidly to the inside by altering conditions on the outside. Storage capacity is at least 10 $\mu g\ cm^{-2}$.

4. Higher alcohols increase the permeability of skin to pyridostigmine, due to a persistent change in skin properties.

5. Technological problems exist in formulating a skin dosing system for pyridostigmine, independently of whether or not the permeability in human skin is sufficient to allow adequate drug through.

6. REFERENCES

1. Shaw, J.E. and Chandrasekaran, S.K. "Controlled Topical Delivery of Drugs for Systemic Action". *Drug Metab. Rev.* 8 (1978) 223-233.

2. Australian National Drug Information Service. "Profile on Glyceryl Trinitrate Ointment 2%". Feb. 1980.

3. Moylan-Jones, R.J., et. al. "The Pharmacokinetics of Pyridostigmine in Humans Part II. Multiple Dose Studies". CDE TP 258 (1979).

4. Ellman, G.L., Courtney, K.D., Andres, V. and Featherstone, R.M. *Biochem. Pharmac.*, 7 88-95. (1961).

5. Tregear, R.T. "Physical Functions of Skin". Academic Press, London, 1966.

6. Dawson, R.M. "Carbamylation and Decarbamylation of Acetylcholinesterase: Effect of Choline, 3,3-dimethyl-1-butanol and some Allosteric Effectors". *J. Neurochem.* 30 (1978). 865-870.

7. Scheuplein, R.J. "Skin Permeation" *in* "The Physiology and Pathophysiology of the Skin". *Ed. Jarret, A.* Vol. 5, p1707. Academic Press, London 1978.

8. Creasey, N.A., Battersby, J. and Fletcher, J.A. "Factors affecting the permeability of skin: the relation between *in vivo* and *in vitro* observations". CDE TN 318, (1977).

TABLE 1

CALCULATION OF THE PERMEABILITY CONSTANT

FOR PYRIDOSTIGMINE ACROSS GUINEA PIG SKIN FROM THE DATA FOR WHOLE ANIMALS

Pyridostigmine concn. mg mL^{-1}	Area of Skin exposed cm^2	Equilibrium ChE activity %	Equivalent infusion rate $\mu g\ h^{-1}$	Steady penetration rate "r" $\mu g\ cm^{-2}\ h^{-1}$	Permeability	Constant "p"
					$cm\ h^{-1}$	$cm\ min^{-1}$
5	20	77	8	0.4	8×10^{-5}	1.3×10^{-6}
50	4	63	20	5.0	10×10^{-5}	1.7×10^{-6}
100	4	38	60	15.0	15×10^{-5}	2.5×10^{-6}

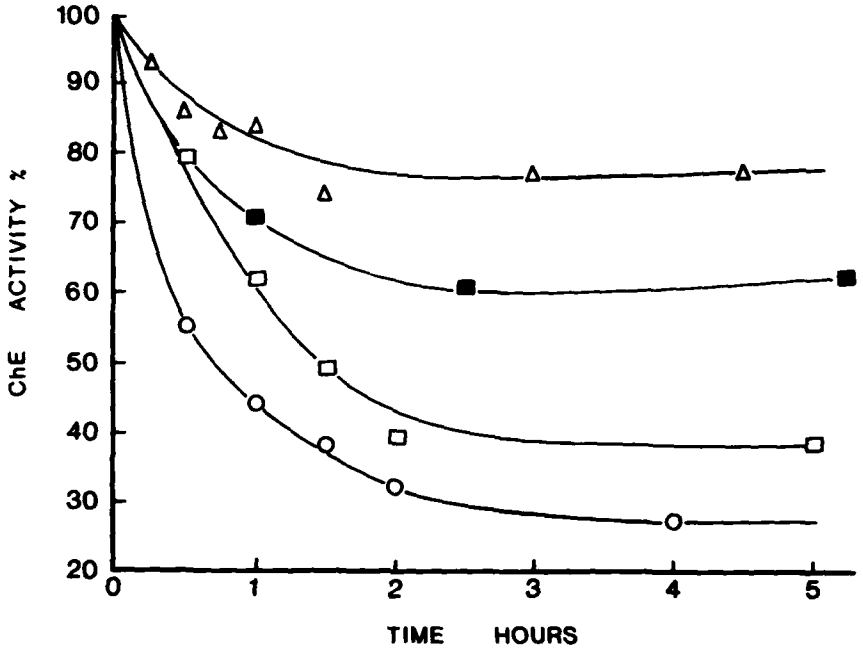

FIG. 1 - Depression of whole blood cholinesterase activity in guinea pigs with time after application of gelled pyridostigmine to the shaven back of the animal. The concentrations of the drug and the contact areas are given.

△ 5 mg/mL, 20 cm^2

□ 50 mg/mL, 4 cm^2

■ 100 mg/mL, 4 cm^2

○ 200 mg/mL, 4 cm^2

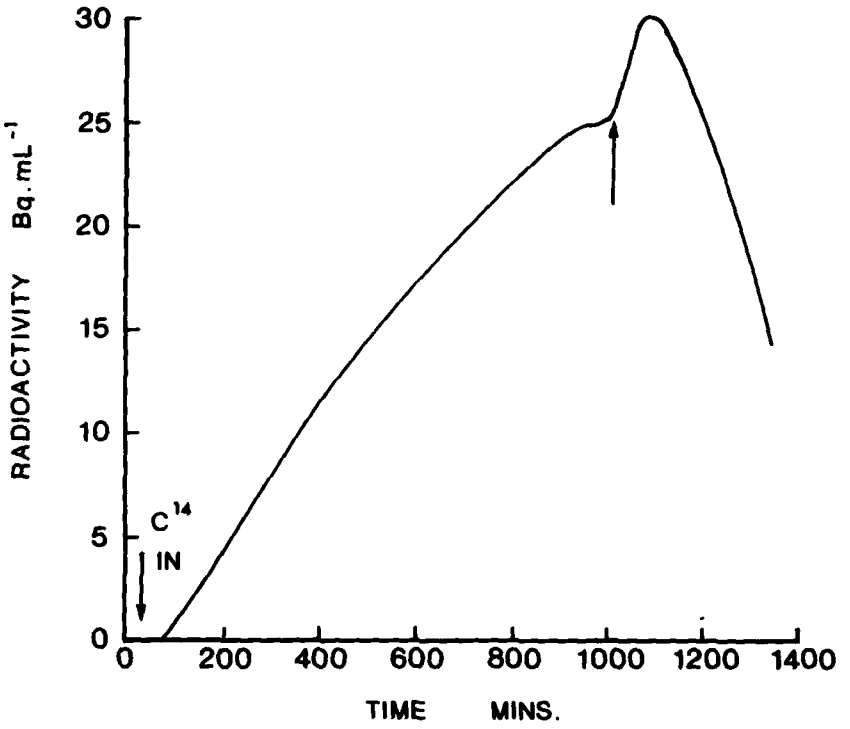

FIG. 2 - The increase in concentration of radioactivity in the circulating fluid of the skin permeation cell as a function of time after application of ^{14}C-pyridostigmine to the epidermal surface. Also shown at ↑ is the result of washing off the radioactive solution with isotonic buffer.

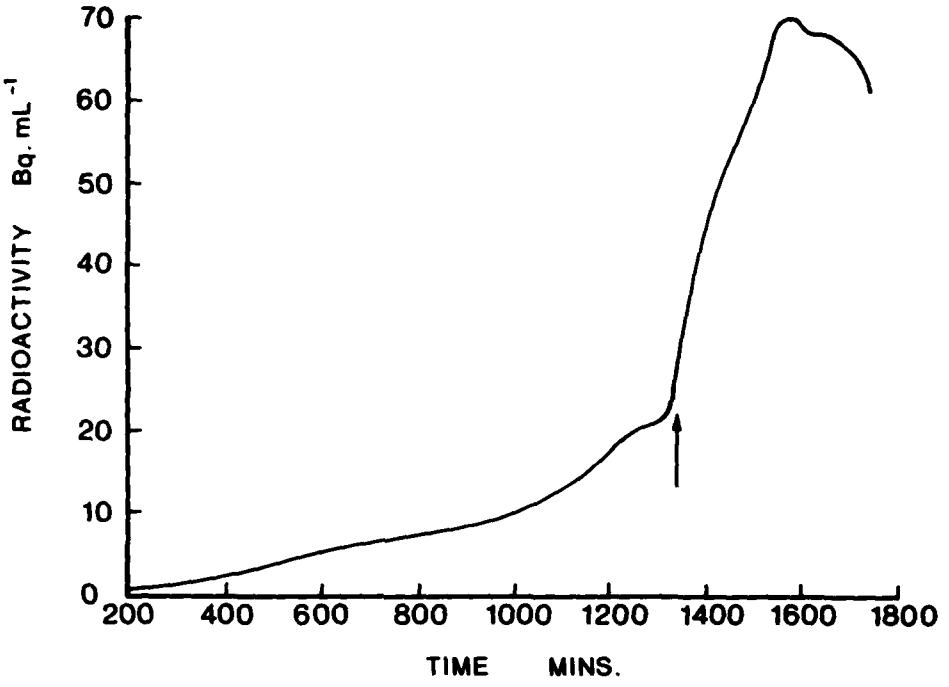

FIG. 3 - A similar experiment to that of Fig. 2, in which the ^{14}C-pyridostigmine was applied in distilled water and washed off with isotonic buffer.

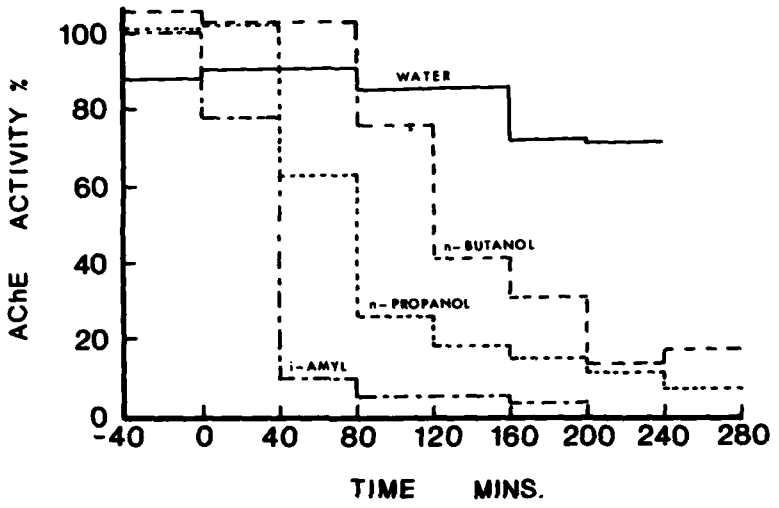

FIG. 4 - Results of several experiments illustrating the depression of AChE activity inside the permeation cell caused by the application of 20 mg mL^{-1} pyridostigmine to the outside. Various alcohols were used as solvents. The line shown for water is the mean of 2 determinations; other results are from single experiments.

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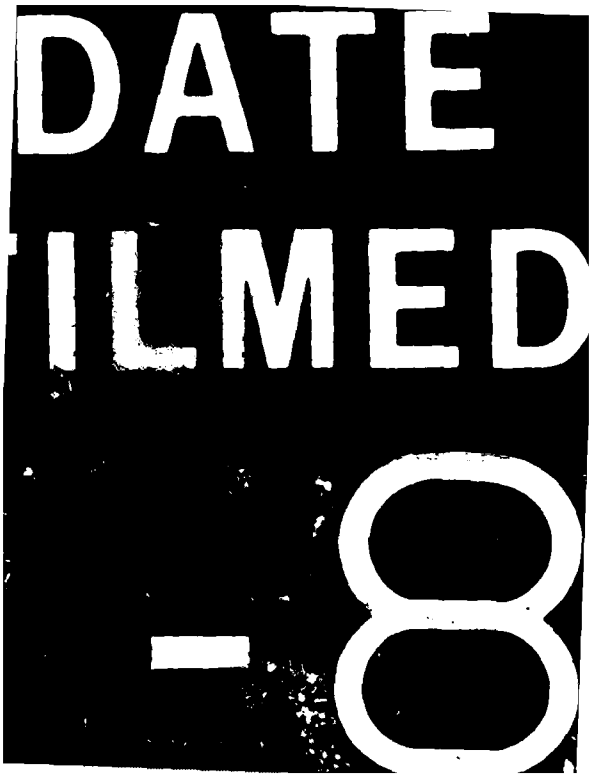
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