DISTRIBUTION OF DIPROPYL [^{35}S]-SULPHOXIDE IN THE RAT

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SUMMARY

Dipropyl [^{35}S]-sulphoxide was administered by gavage (4.24 mmol/kg body weight) to adult male Wistar rats and the placement of radioactivity about the animal examined at 4, 8 and 12 hours post-dosing. Widespread and diffuse distribution throughout soft tissues was observed with the largest amounts of radioactivity being found within the liver (3.2% dose at 4 h) and kidney (1.3% dose at 4 h). Activity levels declined over the 12 hour experimental period. This distribution pattern is discussed and compared with results previously reported for dimethyl sulphoxide.

KEY WORDS

dipropyl sulphoxide, sulphoxide, distribution, rat

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INTRODUCTION

Dipropyl sulphoxide is one member of a homologous series of symmetrical unbranched saturated dialkyl suphoxides which has found use as a thickening agent in paints and cosmetics /1/ and together with dipropyl sulphone has been investigated as an absorption enhancer to aid the passage of heparin across the intestinal mucosa /2/. However, in contrast to the vast amount of knowledge which has been accumulated relating to dimethyl sulphoxide, information concerning the dipropyl compound is virtually absent.

Toxicity observed following the intravenous administration of dipropyl sulphoxide is almost identical to that found with dimethyl sulphoxide. Neurological complications ranging from tremor to convulsions and haemolytic sequelae with injury to blood vessels and oedema were the major problems encountered /3/. Estimates of the LD_{50} values have been quoted at around 500 mg (rat, i.v.) and 900 mg (mice, i.p.) per kilogram body weight /3-5/.

Investigations into the fate of ingested dipropyl [^{35}S]-sulphoxide in rats have indicated that the urine was the major route of excretion with more radioactivity appearing during the second day than the first. Biliary excretion played an important role with about a quarter of the dose passing through the bile duct during two days. Thirteen percent of the dose was still retained within the animal after three days. Metabolism appeared limited to further oxidation, providing dipropyl sulphone and trace amounts of inorganic sulphate /6/.

This study was undertaken to investigate the disposition of dipropyl sulphoxide in the rat and to compare with similar studies previously undertaken with dimethyl sulphoxide.

MATERIALS AND METHODS

Chemicals

Dipropyl sulphide, dipropyl sulphoxide, 1-bromopropane and hydrogen peroxide (30% v/v) were obtained from Aldrich Chemical Co. Ltd (Dorset, U.K.). Sodium sulphide, tetrachloro-1,4-benzoquinone, 1-octanol (capryl alcohol; hplc grade) and water (hplc grade) were supplied by Sigma Chemical Co. Ltd (Dorset, U.K.). All other chemicals were of analytical grade and readily available within the laboratory.

Dipropyl-[^{35}S]-sulphoxide was synthesized from sodium [^{35}S]-sulphide (Amersham International plc, Bucks, U.K.) via dipropyl [^{35}S]-sulphide as previously described in detail /6/. Briefly, 1-bromopropane was refluxed with sodium [^{35}S]-sulphide in aqueous ethanol (70% v/v) for 7-8 hours /7/. After 'salting out' the upper oily layer of dipropyl [^{35}S]-sulphide was purified by distillation (142°C) and then refluxed with aqueous hydrogen peroxide (30% v/v) in acetone for 1 hour /8/. Extraction with petroleum ether (b.p. 40-60°C) removed any unchanged dipropyl sulphide and subsequent evaporation under reduced pressure at 55°C removed the remaining acetone. The resulting solution was dried in a vacuum desiccator over phosphorus pentoxide at 4°C in the dark until the dipropyl sulphoxide crystallized (14-21 days).

The yellow hygroscopic needles (m.p. 14-15°C uncorr.; lit. value 14.5-15.0°C /9/) were harvested and stored at -20°C in nitrogen flushed amber vials. Chemical and radiochemical purities (by t.l.c.) were in excess of 99% with a specific activity of 23.6 mCi/mol (radiochemical yield 65%). The compound displayed strong I.R. absorption bands at 2970 cm^{-1} (n-propyl chain) and 1020 cm^{-1} (sulphoxide) /10-12/. Mass spectral examination gave a top mass ion at m/z 134, a base peak at m/z 43 (propylene) and a fragmentation pattern dominated by alkyl chain fragments /13,14/.

Determination of partition coefficients

Partition (distribution) coefficients between octanol and water (intrinsic lipophilicity) were determined as below. Aliquots (2.5, 5.0, 10.0 μg) of either dipropyl [^{35}S]-sulphide or dipropyl [^{35}S]-sulphoxide were added to a mixture of octanol (50 ml) and water (50 ml) maintained at 25°C, these solvents being mutually saturated before the experiment. The flasks were stoppered and mechanically agitated for 30 minutes. After settling, the liquids were centrifuged (2000 rpm, 90 min) and the radioactivity in each layer determined by scintillation counting as described below /15-17/.

Plasma protein binding

Blood was obtained from anaesthetized adult male rats (Wistar strain, 250 g; National Institute of Medical Research, London, U.K.) by cardiac puncture and centrifuged (3500 rpm, 10 min) in heparinized tubes to provide plasma. Aliquots (2 ml) of plasma were placed into

dialysis tubing ('visking', 15 cm long, 1 cm wide; Fisons Scientific Apparatus, Leics, U.K.) which had been previously sealed at one end and moistened with phosphate buffer (0.1 M, pH 7.4). Dipropyl sulphoxide (20, 30 & 2000 μg) was then added to the plasma which was thoroughly mixed, the tubing sealed and suspended with constant gentle agitation in an outer vessel containing phosphate buffer (30 ml; 0.1 M, pH 7.4). The entire apparatus was maintained at 37°C until equilibrium had been reached (48 hours) /18/. Plasma and buffer samples were taken at regular intervals and counted for radioactivity as described below.

Animal dosing

Dipropyl [^{35}S]-sulphoxide (in distilled water) was administered at the rate of 4.24 mmol (100 μCi) /4 ml /kg body weight by gavage to adult male rats (Wistar strain, 250 g; National Institute of Medical Research, London, U.K.) following an overnight fast. Examination by thin-layer chromatography (silica gel $60GF_{254}$ plates developed in either toluene/acetone [39/1 v/v] or toluene/ethyl acetate [1/1 v/v] /19/) of remnants of the dose solution stored in amber vials at room temperature showed that the sulphoxide was stable for 28 days with decomposition (up to 2%) to unidentified products (not sulphone or sulphide) occurring after 12 weeks /6/.

Whole body autoradiography

Rats were killed by sodium pentobarbitone injection (i.p.) at 12 hours following dosing and the carcasses immersed into a freezing mixture (acetone /solid carbon dioxide) until frozen solid. The animals were then bisected sagittally and encased in carboxymethylcellulose paste which was permitted to solidify at -20°C onto the stage of a microtome cryostat (Bright Instrument Co. Ltd., Huntingdon, U.K.). Sagittal sections were cut, allowed to freeze-dry and then mounted onto transparent adhesive tape. Selected sections were lyophilized for 24 hours before being exposed to X-ray film (Kodak Ltd., Herts, U.K.), the film and section being gently compressed to ensure maximum contact and exposure, before being stored at -20°C in light-proof bags for a period of up to two months /20,21/. Following development, the negatives were visually compared to the appropriate sections and areas of radioactivity noted.

Radioactivity distribution studies

Animals were sacrificed by cervical dislocation at 4, 8 and 12 hours following oral dosing. The major organs were removed by dissection and samples of various tissues taken. Following homogenisation in distilled water, potassium hydroxide (10 M, 2 ml) was added to triplicate aliquots (usually containing 50-100 mg organ/tissue) in separate scintillation vials and left, with periodic mixing, to digest for 7 to 10 days. After this period the samples were decolourised with hydrogen peroxide (30% v/v; 1 ml) and mixed thoroughly with scintillation fluid (Ecoscint; National Diagnostics Ltd, New Jersey, USA). After the decay of chemiluminescence, the vials were counted by liquid scintillation spectrometry (Packard Tricarb 4640; Ambac Industries Inc., Illinois, USA), internal standards being used for quench correction.

Spectrometric methods

Infra-red spectra were obtained by injecting samples in the liquid state, into a sodium chloride cell and placing in the scanning chamber of a Varian Fourier Transform I.R. (Varian Associates, Surrey, U.K.) where all water vapour was removed prior to recording spectra from 800 to 4000 cm^{-1}. Electron impact (E.I.) mass spectrometry was carried out on a Kratos MS80 instrument (Kratos Ltd, Manchester, U.K.) with Kratos D555 (data generator) computerised display and printout facilities. The compound was inserted directly into the ionization chamber at 70 eV with a source temperature of 200°C.

RESULTS AND DISCUSSION

Partition coefficients

Dipropyl sulphide was lipophilic in nature, being at least 800 times more soluble in octanol than water (logP +2.94) whilst dipropyl sulphoxide was around 150 times more soluble in the aqueous phase (logP -2.17), this latter value comparing favourably with that obtained for dimethyl sulphoxide (logP -2.03) /15-17,22/. This calculation of partition coefficients assumes that the solute undergoes no change, neither association nor dissociation, within the solvents. This is probably not the case for dipropyl sulphoxide. It is known that

sulphoxides are hydrogen bond acceptors and form strong hydrogen bonds with water molecules, leading to their hygroscopic nature and ease of solubility in water or protic solvents such as alcohols. Dipropyl sulphoxide was readily soluble in such solvents but was virtually insoluble in diethyl ether, petroleum ether (b.p. 30-40°C) and hexane, liquids in which the sulphide readily dissolved.

Plasma protein binding

Plasma protein binding was unimpressive over the concentration range employed with between 5 and 15% extra remaining within the plasma compartment, presumably protein bound. Human plasma proteins have been shown to bind [^{35}S]-dimethyl sulphoxide /23,24/ with the suggestion that 25% of the dimethyl sulphoxide present in the blood was bound mainly to the albumin fraction /25/. However, other workers have reported that [^{14}C]-dimethyl sulphoxide is not taken up by serum proteins /26/. In comparison to drugs which are avidly bound (e.g. chlorpromazine) such minimal binding is probably of little significance.

Whole body autoradiography and radioactivity distribution studies

Autoradiographs developed from the tissue sections taken from rats twelve hours after oral dosing with [^{35}S]-dipropyl sulphoxide showed that radioactivity was distributed diffusely throughout the majority of the tissue slice. The most concentrated zones of radioactivity were seen within the gut lumen with less intense areas extending into the tissues surrounding the gastrointestinal tract. Radioactivity was also evident within the liver and blood vessels, traces within the lung and no indication within the vertebral column. Similarly, no accumulation of dimethyl sulphoxide in the skeletal system was evident at 24 hours following dosing, but within one hour high concentrations were observed in all bones and structural parts of connective tissue. Otherwise, the patterns observed for the two compounds are very similar /27/.

Immediately after incision into the abdominal cavity of all rats the unmistakable odour of dipropyl sulphoxide was evident, although this quickly dissipated. Overall very small amounts of radioactivity were detected in organs and tissues (Table 1). The largest amounts of radioactivity were found within the liver (3.2 to 0.7%) and the primary organ of excretion, the kidney (1.3 to 0.17%); these levels rapidly

TABLE 1

Distribution of radioactivity amongst organs and tissues following the oral administration of dipropyl [^{35}S]-sulphoxide (4.24 mmol/kg) to male Wistar rats

	Time after oral administration of dipropyl [^{35}S]-sulphoxide		
	4 hours	8 hours	12 hours
ORGAN			
liver	4545 ± 590 [3.20]	1572 ± 106 [1.11]	994 ± 128 [0.70]
spleen	750 ± 56 [0.53]	140 ± 9 [0.10]	61 ± 6 [0.04]
testicles	---	---	162 ± 11 [0.11]
kidney	1846 ± 222 [1.30]	862 ± 54 [0.61]	235 ± 55 [0.17]
heart	558 ± 109 [0.39]	111 ± 5 [0.08]	65 ± 16 [0.05]
lungs	1186 ± 152 [0.84]	297 ± 19 [0.21]	109 ± 38 [0.08]
brain	165 ± 6 [0.12]	99 ± 19 [0.07]	117 ± 23 [0.08]
eye	16 ± 4 [0.01]	> 15 ± 2 [>0.01]	> 15 ± 1 [>0.01]
TISSUE			
fur	22 ± 9 [0.02]	18 ± 11 [0.01]	34 ± 6 [0.02]
skin (ventral)	78 ± 18 [0.05]	92 ± 25 [0.06]	66 ± 12 [0.05]
skin (dorsal)	106 ± 42 [0.07]	65 ± 13 [0.05]	52 ± 10 [0.04]
fat (mesenteric)	60 ± 22 [0.04]	82 ± 26 [0.06]	53 ± 9 [0.04]
fat (perinephric)	45 ± 8 [0.03]	50 ± 6 [0.04]	56 ± 17 [0.04]
muscle	82 ± 30 [0.06]	62 ± 8 [0.04]	51 ± 8 [0.04]

Values are expressed (mean ± sd) as μg of dipropyl [^{35}S]-sulphoxide (or equivalents) in the entire organ or per gram of tissue. Values in square brackets indicate the corresponding mean percentage of administered dose

Detection limit > 15 μg (0.01% dose).
--- indicates not examined

falling over the 12 hour period. Other organs and tissues examined showed minimal levels of radioactivity, with no specific concentration in the brain or eye, the latter organ being previously emphasised as containing higher than plasma levels of dimethyl sulphoxide /27,28/. This overall pattern of widespread and diffuse distribution has been observed during studies concerning the distribution of dimethyl sulphoxide in rats, rabbits, guinea-pigs and mice /25-32/.

These small amounts detected only go a little way to account for the 50% or so of the radioactive dose remaining within the animal after 24 hours which is subsequently excreted /6/. Similar problems of unaccountability have been encountered with quantitative dimethyl sulphoxide distribution studies /33/.

General considerations

The pharmacokinetics of orally administered dipropyl sulphoxide are interesting in that following an initial sharp rise then fall in blood levels, a plateau phase was established (double-peaking) which lasted for 15 to 20 hours /6,34/. An analogous situation has been observed following the cutaneous application of dimethyl sulphoxide in which the compound is rapidly absorbed leading to the establishment of a plateau region which remained almost unchanged for 7 hours in dogs and for 36 to 72 hours in man /27,33/. These plateau regions in the pharmacokinetic profiles are suggestive of retention of the compounds within the body, perhaps in the form of a depot (including delayed absorption from gastrointestinal tract) from which they are released in a slow steady stream into the blood. The sustained low levels of the radioactivity found in the bile and the increased urinary excretion of radioactivity during the second day, both previously reported after oral dipropyl sulphoxide administration, are also suggestive of delayed (variable and discontinuous) absorption from the gastrointestinal tract or transient retention (post-absorptive depot, enterohepatic cycling) within the body /6/. Such events help to detain a compound within the body for much longer than would be expected from simple knowledge of an elimination half-life.

The unaccounted radioactive components must be present in tissues not examined or in specific areas of diffuse tissues (e.g. peritoneal membranes; mesenteric and omental tissues) which were not sampled, and there is a possibility that certain sulphur compounds are associated with lymphoid tissue /35/. If correct, this may be a method of employing a functional group to direct compounds towards and facilitate their retention within the lymphatic system, a potentially desirable factor in chemotherapy. However, lymph nodes have been examined following dimethyl sulphoxide administration and no such associations were evident /27/.

It has been previously stated that dimethyl sulphoxide may be irreversibly bound at a site from which it is slowly converted to

dimethyl sulphone and then excreted /36/. If this were true for the dipropyl homologue such a slow release into the blood stream, maintaining blood levels, may help to explain why levels in the bile remain low but constant over long periods of time /6,37/. Similarly, another group has suggested that the differences in concentration of labelled compound in the soft tissues could be related to that tissue's general metabolic activity /25/.

In common with the present dipropyl homologues, autoradiographs from whole body studies in rats dosed with dimethyl [^{35}S]-sulphoxide showed considerable activity in the gut contents /26/. These workers also noted that the specific activity of faecal samples varied over the 24-hour period and they suggested the possible existence of a faecal dimethyl sulphoxide pool which acted as a reservoir for the recycling of the compound throughout the interstitial spaces of the gastrointestinal mucosa.

Considering the general hydrophilic nature of sulphoxides it is surprising that they are retained, since their highly polar nature would seem to favour rapid urinary excretion. However, owing to the charge separation across the semipolar sulphur-oxygen linkage of sulphoxides, this bond has the ability to interact or associate with various anionic and cationic moieties through both the sulphur and the oxygen atoms of the molecule /38/. Consequently, these molecules may interact more strongly with the protein and lipid environments through which they pass, the oxygen terminal in particular perhaps participating in hydrogen bonding /39-41/. Additionally, certain of these compounds may form aggregations with their own polar zones grouped towards a central core, thus allowing the outer less polar moieties to interact with the more lipophilic cellular components, thereby retarding their overall excretion /41/. Whatever the reasons, the placement of the short chain alkyl sulphoxides within the body remains an intriguing problem.

REFERENCES

1. Tramier B, DeLourme R, Fresel P. Aliphatic sulfoxides as thickeners for oils, paints and cosmetics. Ger Offen 2,450,634. Societe National des Petroles d'Aquitaine, 1975. Chem Abstr 83: 96422.
2. Koh TY. Intestinal absorption of heparin. Can J Biochem 1969; 47: 951-954.
3. Nickson RM, Mitchell SC. Toxicity of dipropyl sulphoxide. Biochem Soc Trans 1992; 20: 211S.
4. Ashwood-Smith MJ. The radioprotective action of dimethyl sulphoxide and various other sulphoxides. Int J Rad Biol 1961; 3: 41-48.

5. Ashwood-Smith MJ. Radioprotective and cryoprotective properties of DMSO. In: Jacob SW, Rosenbaum EE, Wood DC, eds, Dimethyl Sulfoxide. New York: Marcel Dekker, 1971: 147-187.
6. Nickson RM, Mitchell SC. Fate of dipropyl sulphide and dipropyl sulphoxide in rat. Xenobiotica 1994; 24: 157-168.
7. Bost RW, Conn MW. Preparation of n-propyl sulphide. Organic Syntheses 1935; 15: 72-73.
8. Cumper CWN, Reid JF, Vogel AI. Physical properties and chemical constitution. Part XLIV: electric dipole moments of some dialkyl sulphides, disulphides, sulphoxides and sulphones. J Chem Soc 1965: 5323-5330.
9. Winssinger MC. Sur quelques derives du propane. Bull Soc Chim (Paris) 1887; 48: 108-112.
10. Bellamy LJ. In: The Infra-red Spectra of Complex Molecules. London: Methuen, 1954; 295-297.
11. Benedetti E, Santini R, Vergamini P, Chiellini E. Infra-red investigations of the conformational properties of symmetrically substituted dialkyl sulphides. Specrochim Acta 1983; 39A: 57-66.
12. Brunn J, Doerffel S. Die Schwingungsspektren einfacher sulfide, sulfoxide und sulfone im Bereich 500-1500 cm^{-1}. Wissen Zeit Leuna-Merseburg 1971; 13 ser 2: 101- 108.
13. Bowie JH, Williams DH. Studies in mass specrometry XV. Tet 1966; 22: 3515-3525.
14. Smakman R, deBoer TJ. The mass spectra of some aliphatic and alicyclic sulphoxides and sulphones. Org Mass Spect 1970; 3: 1561-1588.
15. Maron SH, Lando JB. In: Fundamentals of Physical Chemistry. New York: Macmillan Publishing Co. Inc, 1974: 465-469.
16. Ives DJC. In: Chemical Thermodynamics. London: Macdonald, 1971: 152-160.
17. Gaillot J, Bruno R, Montay G. Distribution and clearance concepts. In: Hansch C, Sammes PG, Taylor JB, eds, Comprehensive Medicinal Chemistry. Oxford: Pergamon Press, 1990: 71-109.
18. Curry SH. Plasma protein binding of chlorpromazine. J Pharm Pharmac 1970; 22: 193-197.
19. Fishbein L, Fawkes J. Detection and thin layer chromatgraphy of sulphur compounds. 1. Sulphoxides, sulphones and sulphides. J Chromat 1966; 22: 323-329.
20. Ullberg S. The technique of whole body autoradiography. Sci Tools 1977; 28th March (special issue).
21. Franklin ER, Ross DA. Whole body autoradiography. In: Illing HPA, ed, Xenobiotic metabolism and disposition: The Design of Studies on Novel Compounds. Florida: CRC Press Inc, 1989: 41-66.
22. Leo A, Hansch C, Elkins D. Partition coefficients and their uses. Chem Rev 1971; 71: 525-616.
23. Gerhards E, Gibian H, Raspe G. Stoffwechsel und Stoffwechselwirkungen von Dimethylsulfoxide. Arzneimittel-Forsch 1965; 15: 1295-1297.

24. Gerhards E, Gibian H. The metabolism of dimethyl sulfoxide and its metabolic effects in man and animals. Ann NY Acad Sci 1967; 141: 65-67.
25. Denko CW, Goodman RM, Miller R, Donovan T. Distribution of dimethylsulfoxide-^{35}S in the rat. Ann NY Acad Sci 1967; 141: 77-84.
26. Malinin Gl, Fontana DJ, Braungart DC. Distribution of C^{14}-labeled dimethyl sulfoxide in tissues of intact animals. Cryobiology 1969; 5: 328-335.
27. Kolb KH, Janicke G, Kramer M, Schulze PE. Absorption, distribution and elimination of labelled dimethyl sulphoxide in man and animals. Ann NY Acad Sci 1967; 141: 85-95.
28. Kolb KH, Janicke G, Kramer M, Schulze PE, Raspe G. Das Verhalten von ^{35}S Markiertem Dimethylsulfoxid in Menschlichen und Tierschen Organismus. Arzneimittel-Forsch 1965; 15: 1292-1295.
29. Ashwood-Smith MJ. Inability of dimethyl sulphoxide to protect mouse testes against the effect of X-radiation. Int J Rad Biol 1961; 3: 101-108.
30. Hucker HB, Ahmad PM, Miller EA. Physiological disposition and metabolism of dimethyl sulfoxide (DMSO). Fed Proc 1965; 24: 546, abstr 2310.
31. Hucker HB, Ahmad PM, Miller EA. Absorption, distribution, and metabolism of dimethylsulfoxide in the rat, rabbit and guinea pig. J Pharmacol Expt Ther 1966; 154: 176-184.
32. McDermot Gl, Finkbeiner AJ, Zanette B. The fate of dimethyl sulfoxide applied to the skin of the rat. Can J Physiol Pharmacol 1967; 45: 475-478.
33. Wood DC. Fate and metabolism of DMSO. In: Jacob SW, Rosenbaum EE, Wood DC, eds, Dimethyl Sulfoxide. New York: Marcel Dekker, 1971: 133-145.
34. Nickson RM, Mitchell SC. Pharmacokinetics of dipropyl sulphide and its major metabolite. 19th FEBS meeting, Rome 1989; abstr TH171.
35. Phillips JA, Paine AJ. Effect of pyridoxine on the disposition and lymphopenic effects of 2-acetyl-4(5)-tetrahydroxybutyl imidazole in the rat. Xenobiotica 1990; 20: 555-562.
36. Hucker HB, Miller JK, Hochberg A, Brobyn RD, Riordan FH, Calesnick B. Absorption, excretion and metabolism of dimethyl sulfoxide in man. J Pharmacol Expt Ther 1966; 155: 309-317.
37. Nickson RM, Mitchell SC. Biliary excretion of low molecular weight compounds. 11th European Workshop on Drug Metabolism, Konstanz 1988; abstr 2.53.
38. Furukawa N, Fujihara H. Hydrogen bonding and complexing properties of R_2SO_2 and R_2SO. In: Patai S, Rappoport A, Stirling CJM, eds, The Chemistry of Sulphones and Sulphoxides. Sussex: John Wiley & Sons Ltd, 1988; 541-581.
39. Tamres M, Searless S. Hydrogen bonding abilities of cyclic sulfoxides and cyclic ketones. J Am Chem Soc 1959; 81: 2100-2110.
40. Szmant HH. Chemistry of the sulfoxide group. In. Kharasch N, ed, Organic Sulfur Compounds. Oxford: Pergamon Press, 1961; vol 1: 154-169.
41. Mitchell SC. Biological consequences of drug sulphoxidation. Drug Metab Drug Interact 1988; 6: 245-252.