EFFECT OF ACETYLATION AND ROUTE OF ADMINISTRATION ON THE ABSORPTION OF SULPHAPHENAZOLE AND SULPHACETAMIDE SODIUM IN RABBITS

BY

MUNGAI G.K.

Supervised BY

Proffessor C.K. Maitai

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D E D I C A T I O N

This work is dedicated to my parents, Mr and Mrs. J.K Gatarua and the entire family.

A C K N O W E D G E M E N T

I wish to express my sincere gratitude to my supervisor, Proffessor C.K.Maitai for his persistent and very inspiring advice-cum-guidance.

I am extremely grateful for the technical assistance offered by Messrs. Muriithi, Ochieng and Mrs. Wamugunda.

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Finally I must thank my parents, my brothers and my sisters for their collective encouragement, moral and material support throughout my academic persuit.

G.K.Mungai

CONTENTS

A B S T R A C T

This investigation determined the effect of varying route of drug administration on the rate and extent of absorption of sulphacetamide sodium and sulphaphenazole in rabbits. The N^4-acetyl derivatives of both sulphacetamide and sulphaphenazole were also administered as follows;-

(i) acetyl sulphacetamide was administered both orally and intravenously.

(ii) acetyl sulphaphenazole was administered orally. Unconjugated sulphaphenazole was also administered orally for comparison.

The aim of administering the acetylated sulphonamides was to establish the possible effects of acetylation on the absorption of both sulphacetamide and sulphaphenazole.

Five different routes of administration were investigated namely oral, intravenous, subcutaneous, intramuscular and intraperitoneal routes.

The plasma clearance of sulphacetamide was determined and compared with that of acetyl sulphacetamide. This was done by administering equivalent doses of sulphacetamide and its acetyl derivative to different rabbits. Blood samples were obtained at predetermined times after drug administration and analysed for both sulphacetamide and acetyl sulphacetamide.

The bioavailability of sulphaphenazole when administered orally was compared to that of its acetyl derivative basing the comparison on the level of sulphaphenazole attained in plasma with time after drug administration.

Results of this investigation showed that,
The absorption rate of sulphacetamide sodium was in the order iv> ip > im >sc >oral route.
It was also established that sulphacetamide has a higher plasma clearance than its acetyl derivative and that acetylation retarded the absorption of sulphaphenazole.

Similarly, it was evident that orally administered sulphaphenazole produces high and stable plasma concentration of the drug such that the dosing frequency is not as high as for other sulphonamides. It is therefore a long acting sulphonamide.

I N T R O D U C T I O N

The concentration of a drug in the body after administration depends on many factors such as, dose and route of administration, rate and limitations of absorption, distribution in the body, and rate of degradation and excretion (1). The determination of amounts of sulphonamides in body fluids and tissues has been of great importance because it provides a useful way of evaluating the doses for therapy. The availability of such data is limited by lack of adequate animal models especially in the development of new sulphonamides and pre-formulation studies.

Before carrying out a study of the bioavailability of sulphonamides, it is important to consider the various factors that influence the observed plasma concentrations i.e.

Absorption

Except for enteric sulphonamides, this class of drugs is rapidly and adequately absorbed from the gastro-intestinal tract. The small intestine is the major site of absorption but some of the drug is absorbed from the stomach. Although local application of sulphonamides is still in use, this should be discouraged because this application is not successful in controlling infections of skin or mucous membranes and such therapy results in toxic reactions, particulary allergic reactions.

Absorption of sulphonamides may be influenced by concurrently administered drugs or compounds. Hayton, W.L. (2) studied the effect of several alcohols on the absorption of sulphapyridine using 0.5% solution of the alcohols. He was able to show that ethanol did not significantly affect drug absorption. Both butanol and hexanol reduced the rate of absorption of sulphapyridine.

Biovailability of sulphonamides is also influenced by the dissolution behaviour of the sulphonamide.

Mathur et al(3) using human subjects investigated the relationship between bioavailability and dissolution behaviour of sulphadiazine.

Significant correlation was obtained between maximum plasma concentration of sulphadiazine and % sulphadiazine dissolved in 30 minutes.

Distribution

Sulphonamides are distributed throughout all tissues and body fluids. The drug readily enters pleural, peritoneal, synovial and ocular fluids. The protein content of such fluids is usually low and the drug mostly exists in the unbound active form. The sulphonamides readily pass across the placeta and reach the fetal circulation. The concentrations attained in the foetal tissues are sufficient to cause toxic effects. Goodman, L.S. and Gilman, A. (1) determined the fetal blood level of sulphadiazine to be 50-90% of that in the maternal circulation.

Protein Binding

All sulphonamides are bound in varying degrees to plasma proteins. The extent of binding is almost directly proportional to the concentration of albumin in the plasma. In general, acetylated sulphonamides are bound to a greater extent than their corresponding free form. The bound fraction is not available for renal excretion and acts as a drug reservoir. The extent of protein binding that any given sulphonamide exhibits will influence the plasma concentration measured after its administration. Mathur et al (3) investigated the effect of serum protein binding on sulphisoxazole distribution, metabolism and excretion in rats. Serum protein binding was found to be a major determinant of the intersubject differences in sulphonamide excretion and biotransformation kinetics.

In his work, Ritschel, W.L. (8) carried out a comparative study of the binding of sulphaphenazole to fetal, neonatal and adult human plasma albumin. He established that, in man, sulphaphenazole has a lower affinity for the albumin of the fetus and neonate than for that of the adult. Removal of bound endogenous anions from neonatal albumin by treatment with charcoal at PH 3.0 restored the affinity of the protein for sulphaphenazole to the adult level. Prior treatment of adult albumin with bilirubin reduced the affinity of the protein for sulphaphenazole to that observed in fetal and neonatal albumins. Thus, the reduced affinity of sulphaphenazole for fetal and neonatal albumin is the result of the presence of a tightly bound endogenous ligand, such as bilirubin on fetal and neonatal albumin.

Metabolism

The rate of metabolism will also determine the plasma level achieved after administration of a standard dose of sulphonamide. The major routes of metabolism are acetylation and oxidation. Acetylation is disadvantageous because the metabolite has no antibacterial activity but retains the toxic effects of the parent sulphonamide. Furthermore, the acetylated forms of certain sulphonamides are less solude and hence contribute to crystalluria and renal disorders. It is therefore important to know the status of renal function in patients given sulphonamides.

Excretion

The rate of excretion influences the drug plasma level because sulphonamides are largely excreted in the urine partly as unchanged drug and partly as metabolic products. Small amounts are eliminated in the faeces, bile and milk.

Interaction of Sulphonamides with other drugs

This is another factor that can alter the observed plasma concentration of sulphonamides. Levy et al (6) has studied the effect of sulphisoxazole on the pharmacokinetics of free and plasma protein bound bilirubin.

They obtained results that were consistent with the recently developed pharmacokinetic theory according to which, the plasma clearance of total bilirubin should increase upon administration of a displacing agent while the plasma clearance of free bilirubin should remain unchanged. Bilirubin induced encephalopathy caused by sulphisoxazole or other displacing agents may be due to very transient elevated plasma concentrations of total bilirubin and the consequent redistribution of the pigment to extravascular sites including the brain.

Martindale (7), established the following interactions of sulphaphenazole with other concurrently administered drugs

(i) sulphaphenazole prolongs the serum half-life of benzyl penicillin.

(ii) sulphaphenazole reduces the protein binding and increases the half-life of sulphonyl urea compounds for example chlor propamide.

(iii) sulphaphenazole and its methyl and ethyl derivatives increase the half-life of tolbutamide.

In the present work, two sulphonamides, sulphacetamide sodium and sulphaphenazole have been studied. Sulphaphenazole is readily absorbed from the gastro intestinal tract and is bound to plasma albumin to the extent of 80% or more (1). Work done by Ritschel, W.L. (8) established that sulphaphenazole is cetylated in the liver to an extent of approximately 12-16% and is slowly excreted. Within 8 hours, 21% of the administered dose was excreted in urine, 30% being conjugated. Free and conjugated sulphaphenazole had the same solubility. The biological half-life was reported as 8-12 hours.

The objective is to study the effect of varying route of drug administration on the absorption of sulphacetamide sodium and also investigate the effect of Θ- N^4- Acetylation of both sulphacetamide sodium and sulphaphenazole on absorption in rabbits.

The extent of absorption was estimated on the basis of the plasma concentration achieved after administration. A colorimetric method was employed for the analysis of sulphacetamide sodium (13).

E X P E R I M E N T A L

CHEMICALS AND REAGENTS

CHEMICAL OR REAGENT	GRADE	SUPPLIER
Sulphacetamide sodium B.P.	Lab. grade	May & Baker
Trichloroacetic acid	Lab. grade	Merck
Sodium nitrite	Lab. grade	BDH Chemicals Ltd.
Ammonium sulphamate	Lab. grade	SDS Chemicals Ltd.
N-(1-naphthyl)ethylene diamine dihydrochloride	Lab. grade	Merck
Heparin Injection B.P. (5000 units/ml)		
Sulphaphenazole tablets 500mg (SUTA)	Manufactured by Ciba	
Acetic anhydride	Lab. grade	BDH Chemicals Ltd.
Anhydrous sodium acetale	Lab. grade	BDH Chemicals Ltd.
Conc. H_2SO_4	Analytical grade	KEL Chemicals Ltd.
Pyridine	Lab. grade	BDH Chemicals Ltd.
NaOH pellets	Analytical grade	BDH Chemicals Ltd.
Vaseline petroleum jelly		

GLASSWARE AND OTHER MINOR APPARATUS

Light bulldog clips
Blood collecting vials
0.2 ml blood pipette
Sterile syringes and needles
Round bottomed flask
Water bath
Test tubes
1, 2 and 5 ml graduted pipettes
Dropper with a teat

EQUIPMENT	SUPPLIER
Spectrophotometer SP 8000	Pye Unicam
Bausch and Lomb● Spectronic 21	KLSC Ltd.
Centrifuge	MSE Ltd.

METHODS

1. ASSAY OF SULPHACETAMIDE SODIUM IN BLOOD

Blood samples were taken from the marginal ear vein of the rabbit. The edge of the ear was shaved and smeared with vaseline petroleum jelly, so that the blood run freely over the surface into a blood collecting vial. The animal was given an intravenous injection of heparin at a dose of 1000 units/kg body weight of the rabbit. Bleeding from the site of injection was controlled by applying a small piece of cotton wool and a light bulldog clip. The animal was kept warm, particularly the ears which were gently heated with a lamp for some minutes before any blood sample was taken. The clip and cotton wool were replaced after the sample had been taken. Samples were collected over a period of 2 hours. The first 2 or 3 drops were discarded, particularly if the ear had not been kept warm and there was reason to believe that the circulation in the ear had been poor. If the animal had received the drug intravenously in one ear vein the blood samples were taken from the other ear vein. 0.2ml samples of blood were measured with a 0.2ml blood pipette and treated as follows:

The 0.2ml sample of blood was added to 3.2ml distilled water in a testtube and the blood pipette washed by sucking some of the water in and blowing it out again. The blood and water were mixed by shaking gently and leaving them for 5 minutes. 0.6ml of 25% w/v trichloroacetic acid was added using a 1ml pipette and the tube shaken vigorously and intermittently for 5 minutes. The precipitated protein was separated by centrifuging for 5 minutes. 2.0ml of the supernatant was transferred to another dry tube using a 2ml pipette 2 drops of 0.5% w/v sodium nitrite was added using a dropper, the tube shaken and left for 3 minutes. 1.0ml of 0.5% w/v ammonium sulphamate was added using a 1ml pipette to destroy the excess nitrous acid and the tube shaken intermittently for 2 minutes. 2.0ml of a 0.05% w/v N-(1-naphthyl) ethylene diamine dihydrochloride was added using a 2ml pipette and the tube shaken.

The colour was fully developed after 5 min. and did not fade appreciably over a period of one hour. The optical density was measured at 540nm using spectrophotometer SP 8000.

It was necessary to prepare standard solutions of sulphacetamide in order to obtain a calibration graph of optical density against concentration. The concentrations chosen were in the range 20-200mg/litre and 0.2ml samples of these were treated as described above for the blood samples.

Blood samples were obtained from 5 rabbits which has been administered with a dose of sulphacetamide sodium, 150mg/kg through either of the following routes: subcutaneously, intramuscularly, intravenously, intraperitoneally and orally. Blood samples were taken before drug administrion, and then 10, 30, 60, 90 and 120 min. after the administration of drug. The sample taken before the administration of the drug served as blank. From the calibration graph, the concentration in blood was determined and plotted against time.

2. ASSAY OF SULPHAPHENAZOLE IN BLOOD

0.2ml sample of blood was measured with a blood pipette and added to 4.2ml of distilled water in a test tube. The pipette was washed by sucking some of the water in and blowing it out again. The blood and water were mixed by shaking gently and leaving them for 5 min. 0.6ml of 25%w/v trichloroacetic acid was added using a 1ml pipette and the tube shaken vigorously and intermittently for 5min. The precipitated protein was separated by centrifuging for 5 min. The absorbance of the supernatant solution was read at 295mm using the spectronic 21. The sample taken before the administration of the drug served as the blank.

Standard solutions of sulphaphenazole were prepared in order to obtain a calibration graph of optical density against concentration. The concentrations chosen were in the range 83.3-1250mg/litre and were prepared as follows: A quantity of powder equivalent to 5 tablets of sulphaphenazole was dissolved in 2 litres of distilled water, shaken vigorously to dissolve the drug and filtered to obtain the drug solution.

The concentration of the resultant solution was 1.25 mg/ml. This solution was diluted by factors of 15, 10, 5, 3, and 1 to give the desired range of concentration above. The absorbance of the solutions was measured at 295 nm using the spectronic 21.

A dose of sulphaphenazole, 100 mg/kg was orally administered to a rabbit. Blood samples were taken before the administration, and subsequently 10, 30, 60, 90 and 120 min. after administration of the drug. The sample taken before the administration of the drug served as blank. From the calibration graph, the concentration of sulphaphenazole in blood was determined and plotted against time.

3. ASSAY OF ACETYL SULPHACETAMIDE SODIUM AND ACETYL SULPHAPHENAZOLE IN BLOOD

As acetyl sulphacetamide and acetyl sulphaphenazole were not available, it was necessary to prepare them. The detailed methods for the preparation of both acetyl sulphacetamide and acetyl sulphaphenazole and for the hydrolysis of the acetyl derivatives in blood back to their non-acetylated forms can be obtained from the work of Dr. William Kemp (11), work by Karl et al (14) and Morrison, R.T. and Boyd, R.N. (12).

In the assay of acetyl sulphacetamide, 0.2 ml blood sample was measured using a 0.2 ml blood pipette. The sample was treated in the same way as in the assay of sulphacetamide sodium up to the point where the precipitated protein is separated by centrifugation. 2 ml of 67% H_2SO_4 was added to 2 ml of the supernatant solution using a 2 ml pipette. The solution was heated in a boiling water bath for 20 min. and the solution allowed to cool. 2 drops of 0.5 % w/v solution of sodium nitrite was added using a dropper, the tube shaken and left for 3 min. 1.0 ml of 0.5% w/v ammonium sulphamate was added using a 1 ml pipette and the tube shaken intermittently for 2 min. 2.0 ml of o.o5% w/v solution of N-(1-naphthyl) ethylene diamine dihydrochloride was added and the tube shaken. The optical density of the resultant solution was measured at 540 nm.

using the SP 8000 spectrophotometer.

In assaying sulphaphenazole in blood, 2 ml of 67% H_2SO_4 was added to 2 ml of the supernatant solution using a 2 ml pipette. The solution was heated in a boiling water bath for 20 min. and then allowed to cool. The absorbance of the solution was measured at 295 nm using the spectronic 21 instrument.

R E S U L T S

The following table shows valves for optical density and concentration of sulphacetamide sodium used to plot the standard curve (fig.1) for determination of sulphacetamide in blood.

Table 1.

Concentration of Sulphacetamide (mg/l)	Optical Density at 540 nm (on SP8000)
20	0.08
40	0.18
60	0.24
80	0.31
100	0.36
120	0.45
140	0.54
160	0.62
180	0.71
200	0.84

The valves for optical density were read directly from the spectral chart (fig2) which is typical of all other charts obtained in the analysis of sulphacetamide samples.

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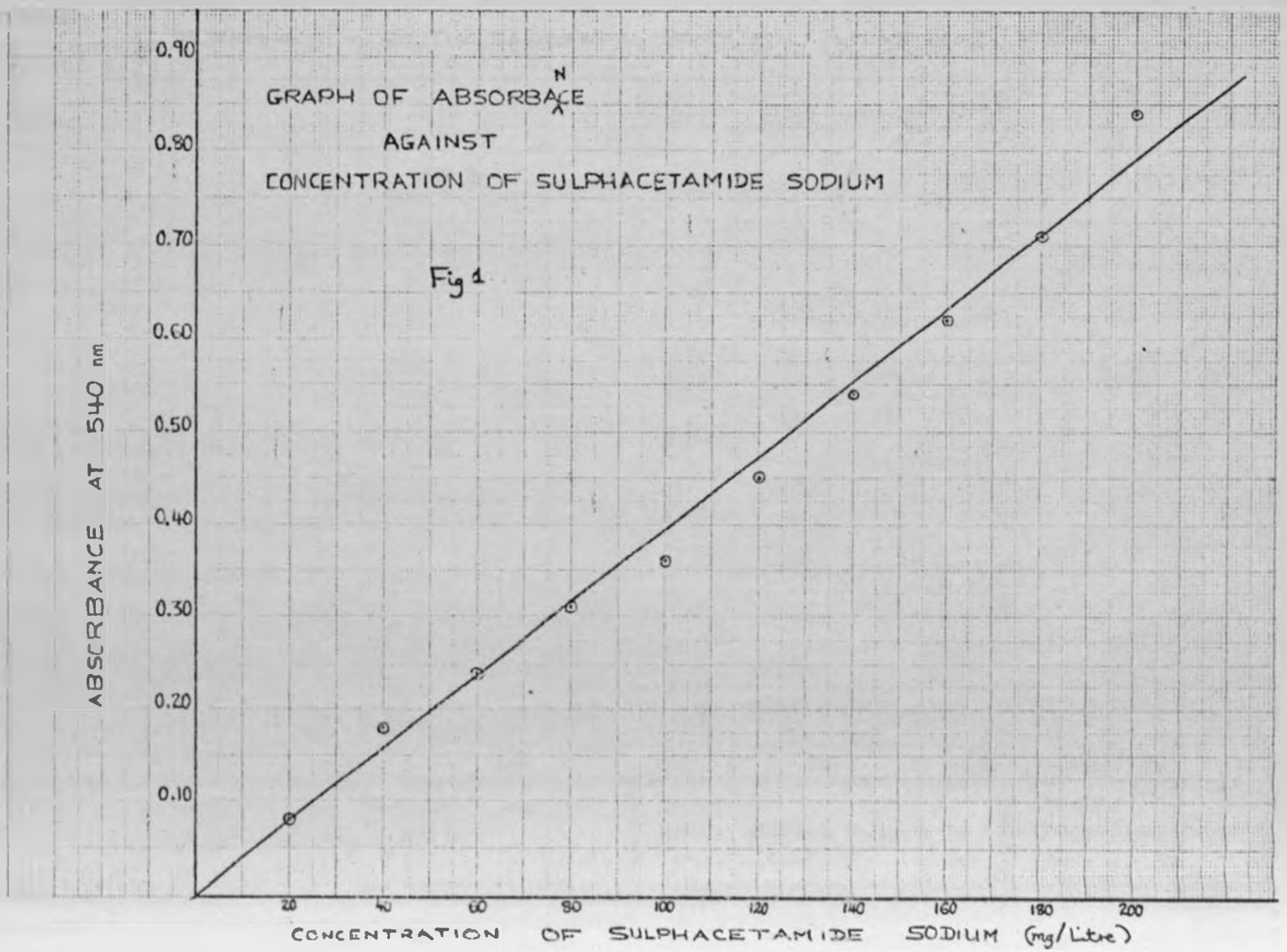
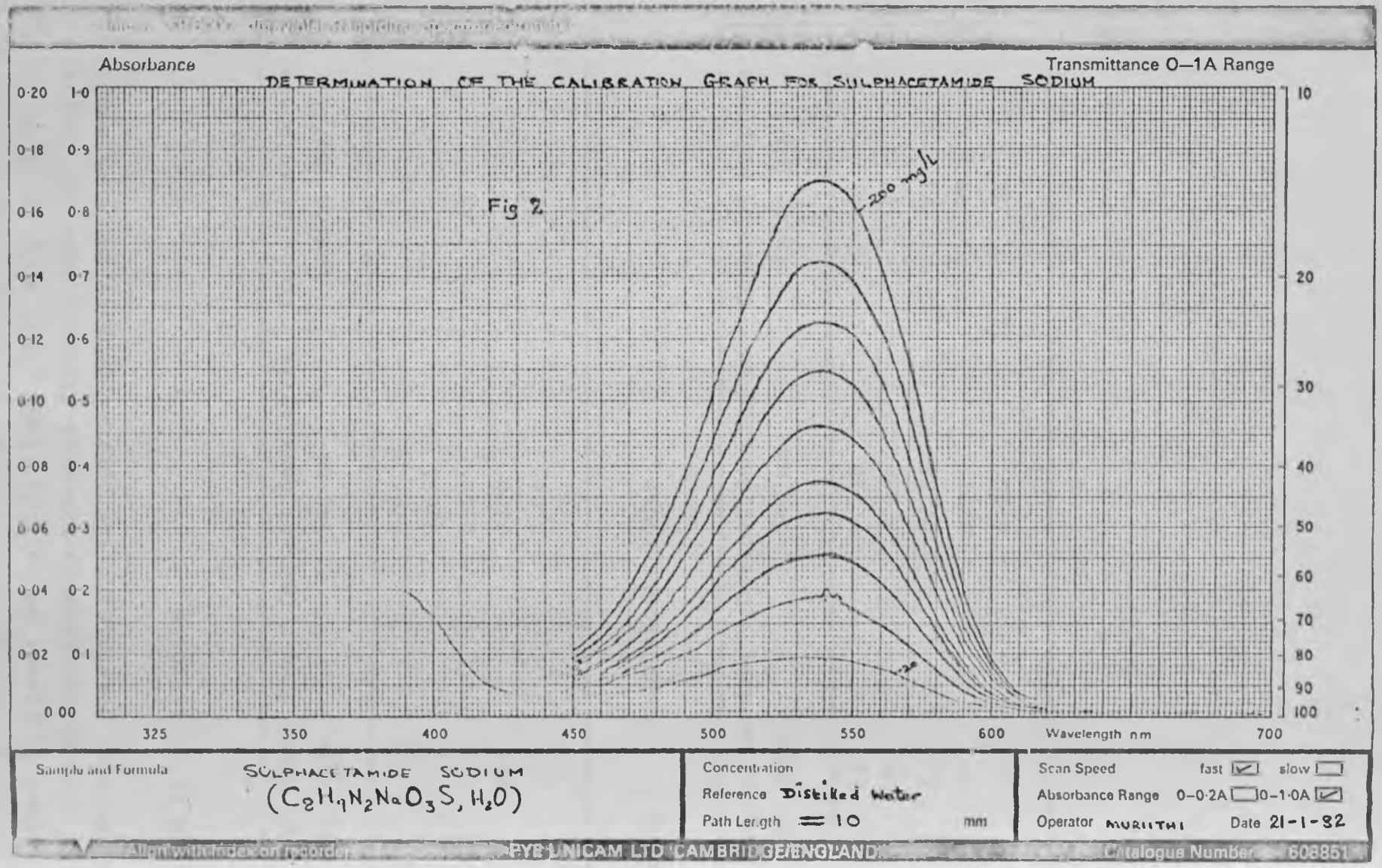

GRAPH OF ABSORBANCE
AGAINST
CONCENTRATION OF SULPHACETAMIDE SODIUM
Fig 1
ABSORBANCE AT 540 nm
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
20
40
60
80
100
120
140
160
180
200
CONCENTRATION OF SULPHACETAMIDE SODIUM (mg/Litre)


Absorbance
Transmittance 0—1A Range
DETERMINATION OF THE CALIBRATION GRAPH FOR SULPHACETAMIDE SODIUM
Fig 2
200 mg/L
20
0·20 1·0
0·18 0·9
0·16 0·8
0·14 0·7
0·12 0·6
0·10 0·5
0·08 0·4
0·06 0·3
0·04 0·2
0·02 0·1
0·00
10
20
30
40
50
60
70
80
90
100
325 350 400 450 500 550 600 Wavelength nm 700
Sample and Formula
SULPHACETAMIDE SODIUM
$(C_8H_9N_2NaO_3S, H_2O)$
Concentration
Reference Distilled Water
Path Length = 10 mm
Scan Speed fast ☑ slow ☐
Absorbance Range 0–0·2A ☐ 0–1·0A ☑
Operator MURUTHI
Date 21-1-82
All rights with Hitachi Perkin Elmer Ltd
PYE UNICAM LTD CAMBRIDGE ENGLAND
Catalogue Number 603851

Tables 2-6 show the concentrations of sulphacetamide sodium attained in plasma at various times after drug administration N.B. The concentrations are read directly from the standard curve after determining the optical density for each sample.

Table 2: oral route

Time after drug adm. (min.)	Optical density at 540 nm	Conc. of sulphacetamide (mg/l)
13	0.02	5
30	0.035	9
60	0.10	25
104	0.08	20
125	0.065	17

Table 3: Subcutaneous route

Time after drug adm. (min)	Optical density at 540 nm	Conc. of sulphacetamide (mg/l)
11	0.230	59
31	0.380	97
62	0.365	93
95	0.31	79
122	0.30	76

Table 4: Intraperitoneal route

Time after drug adm. (min)	Optical density at 540 nm	Conc. of sulphacetamide (mg/l)
10	0.455	116
30	0.645	164
62.5	0.695	176
96	0.615	156
122	0.545	138

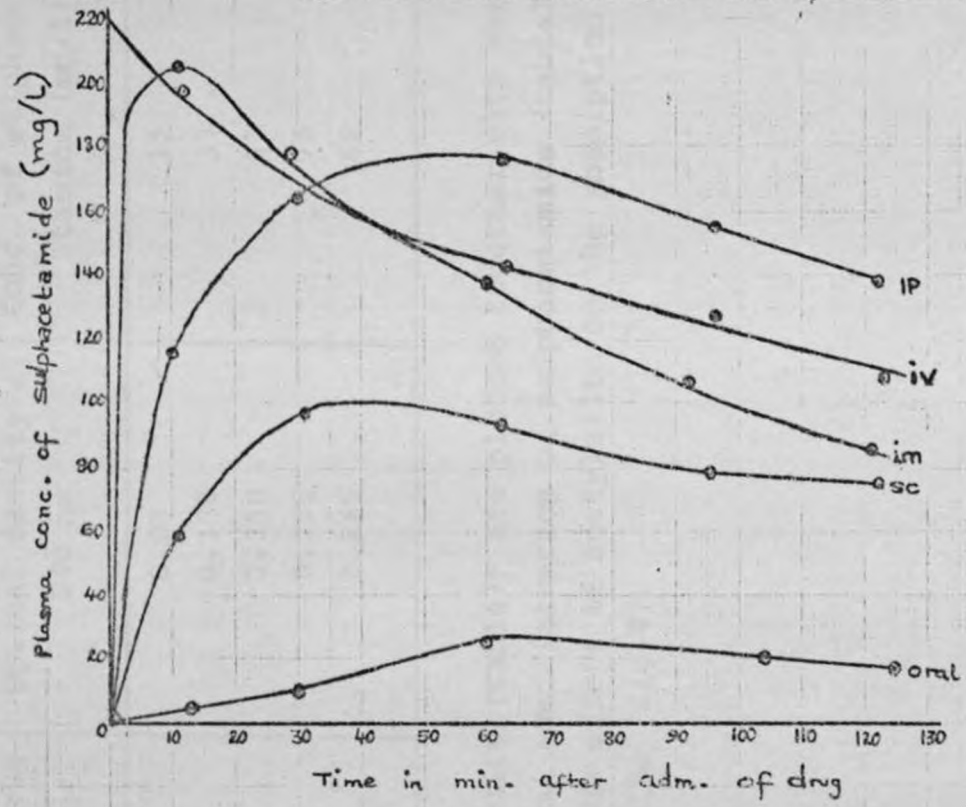
Table 5: Intravenous route

Time after drug adm. (min)	Optical density at 540nm	Conc. of sulphacetamide (mg/l)
12	0.780	198
29	0.70	178
60	0.545	138
92	0.420	107
121	0.340	86

Table 6: Intramuscular route

Time after drug adm. (min)	Optical density at 540 nm	Conc. of sulphacetamide (mg/l)
11	0.815	206
30.5	0.640	162
63	0.565	143
96	0.505	128
123	0.465	118

Fig. 3 Graph showing the absorption of sulphacetamide sodium through different routes of adm. of a standard dose.



Key
IP → intraperitoneal
Im = intramuscular
iv = intravenous
SC = subcutaneous

Table 7:

Results for concentration of acetyl sulphacetamide attained in plasma against time after oral administration.

Time after drug adm. (min)	Optical density at 540 nm	Conc. of sulphacetamide (mg/l)
10	0.06	15
31	0.130	33
60	0.250	63
91	0.295	75
122	0.265	68

These results (table7) are plotted together with the results for oral administration of sulphacetamide (table2) to determine the effect of acetylation on the absorption of sulphacetamide (fig 4).

Fig. 4 Plasma concentration of sulphacetamide against time after oral administration.

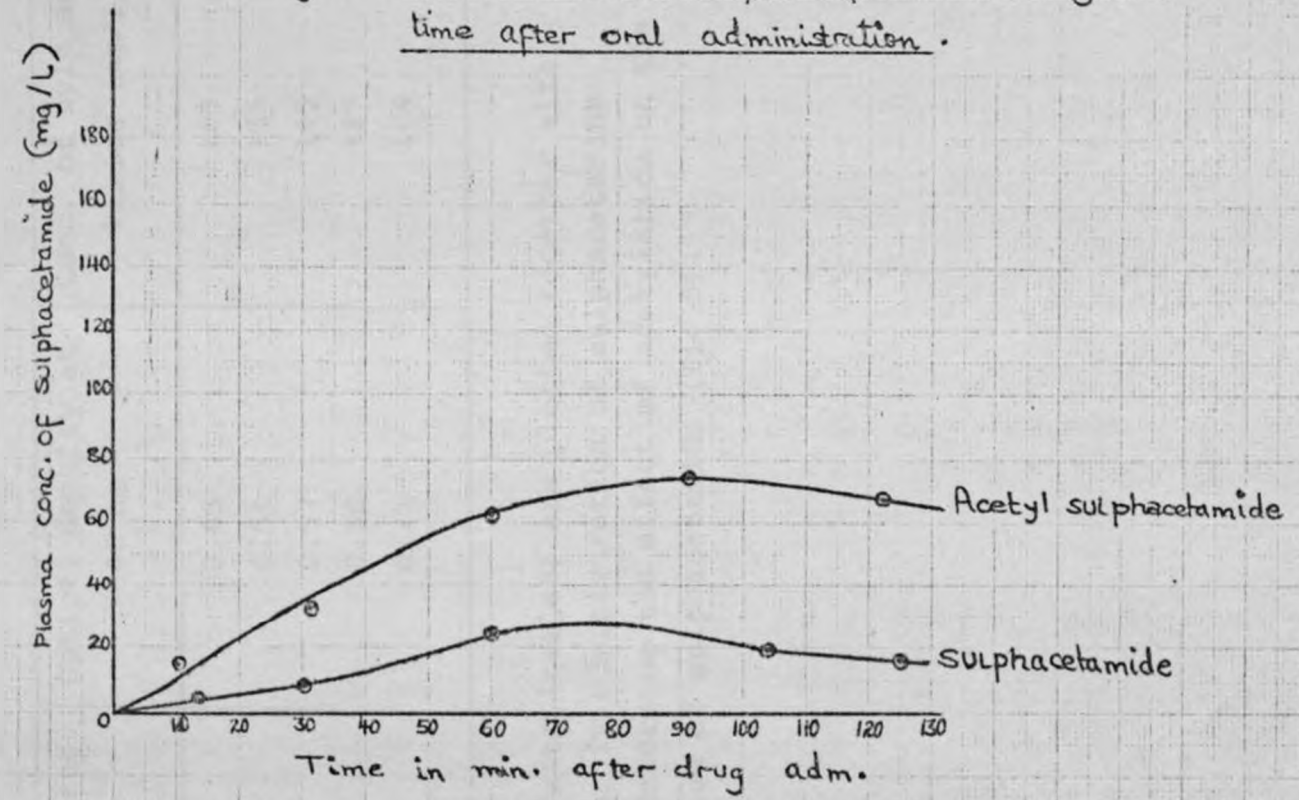


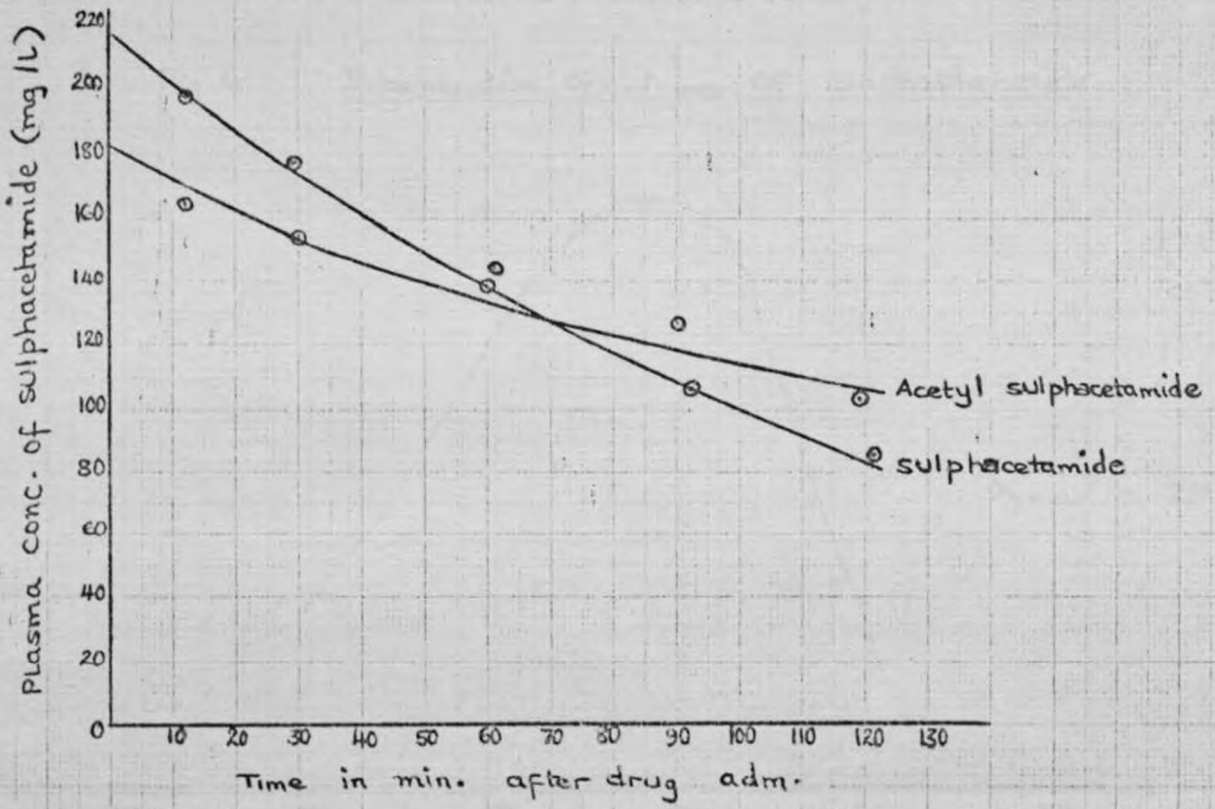
Table 8:

Results for concentration of acetyl sulphacetamide attained in plasma against the time after iv administration of acetyl sulphacetamide.

Time after drug adm. (min)	Optical density at 540 nm	Conc. of sulphacetamide (mg/l)
12	0.65	165
30	0.61	155
61	0.57	145
90	0.50	127
119	0.41	104

These results (table8) are plotted together with the results for iv administration of sulphacetamide (table 5) to determine the effect of acetylation on the plasma clearance of sulphacetamide (fig 5).

Fig. 5 Plasma concentration of sulphacetamide against time after iv administration of drug.



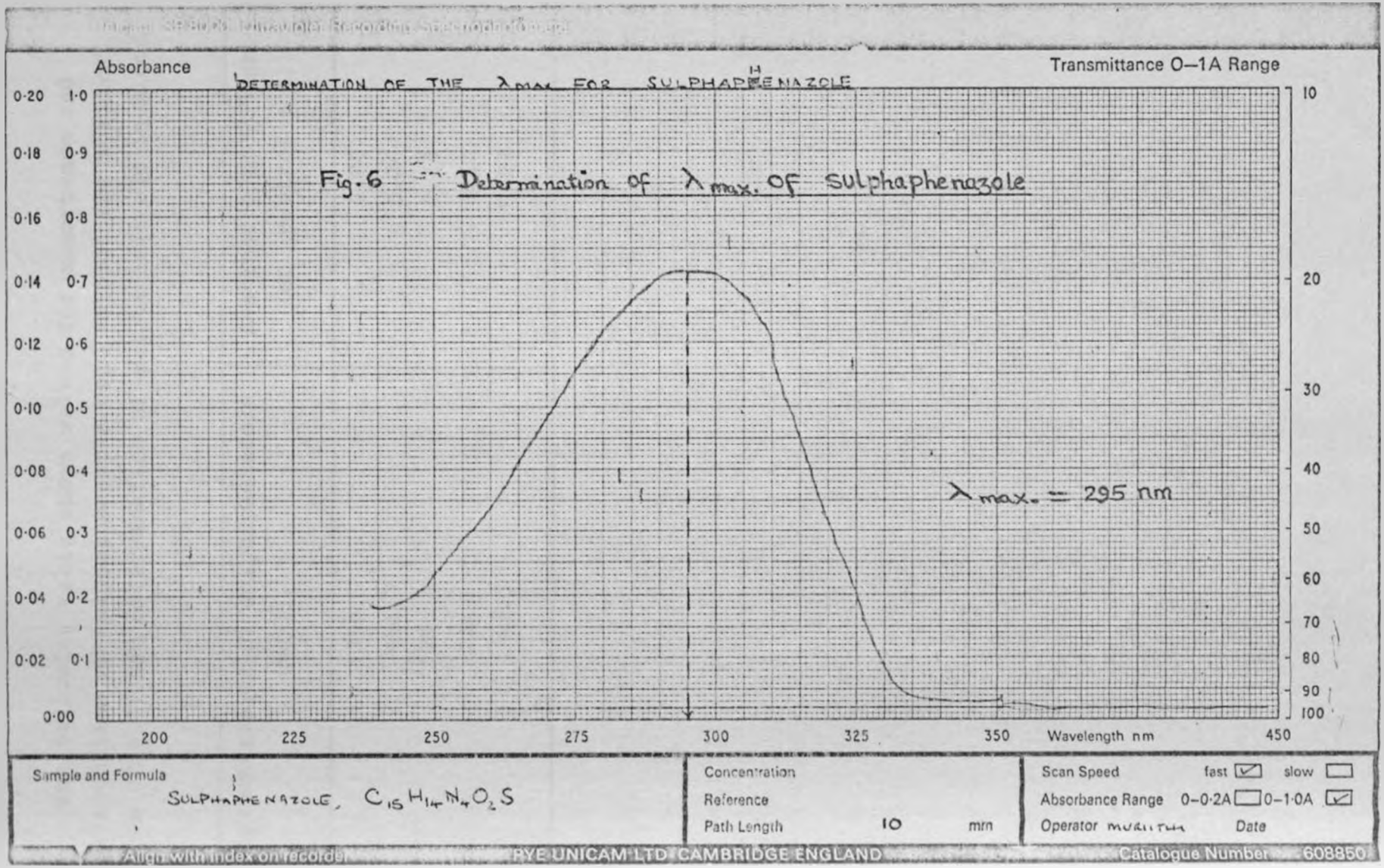

Absorbance
Transmittance 0—1A Range
DETERMINATION OF THE λmax FOR SULPHAPHENAZOLE
Fig.6 — Determination of λmax. of sulphaphenazole
λmax. = 295 nm
0·20 1·0
0·18 0·9
0·16 0·8
0·14 0·7
0·12 0·6
0·10 0·5
0·08 0·4
0·06 0·3
0·04 0·2
0·02 0·1
0·00
10
20
30
40
50
60
70
80
90
100
200 225 250 275 300 325 350 Wavelength nm 450
Sample and Formula
SULPHAPHENAZOLE, $C_{15}H_{14}N_4O_2S$
Concentration
Reference
Path Length 10 mm
Scan Speed fast ☑ slow ☐
Absorbance Range 0–0·2A ☐ 0–1·0A ☑
Operator MUKHTAR Date
Align with index on recorder
RYE UNICAM LTD CAMBRIDGE ENGLAND
Catalogue Number 608850

Table 9:

The following table shows valves for absorbance and concentration of sulphaphenazole used to plot the standard curve (fig 7) for determination of sulphaphenazole in blood.

Concentration of sulphaphenazole (mg/l)	Absorbance at 295 nm. (on spectronic 21)
1250	0.88
416.7	0.26
250	0.13
125	0.10
83.3	0.07

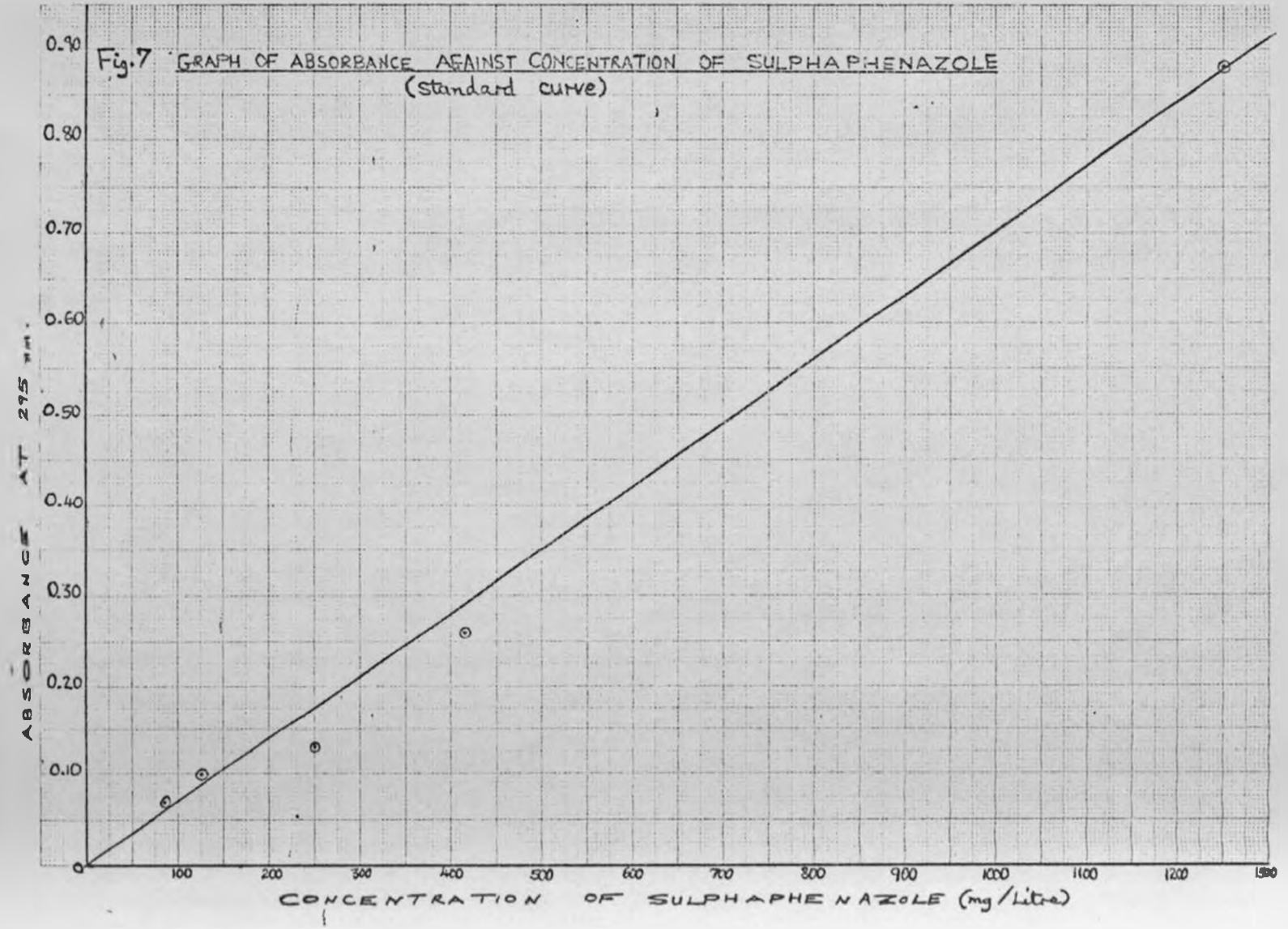


Fig.7 GRAPH OF ABSORBANCE AGAINST CONCENTRATION OF SULPHAPHENAZOLE
(standard curve)
ABSORBANCE AT 295 mm.
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0
100
200
300
400
500
600
700
800
900
1000
1100
1200
1300
CONCENTRATION OF SULPHAPHENAZOLE (mg/Litre)

The following tables show the plasma concentration of sulphaphenazole determined at different times after oral administration of (1) Sulphaphenazole and
(11) acetyl sulphaphenazole

Table 10: Plasma concentration of sulphaphenazole after oral administration

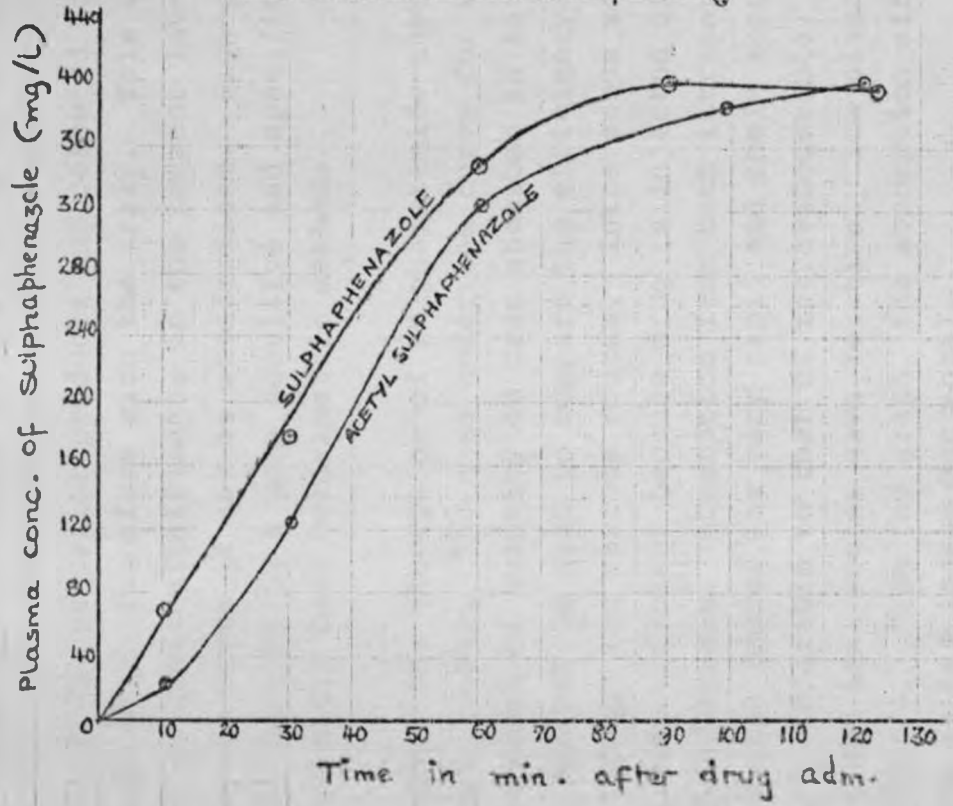
Time after oral adm. (min)	Absorbance at 295nm	Conc.of sulphaphenazole (mg/l)
10	0.05	70
30	0.125	180
60	0.245	350
90	0.280	400
123	0.275	395

Table 11: Plasma concentration of sulphaphenazole after oral administration of acetyl sulphanazole

Time after drug adm. (min)	Absorbance at 295nm	Conc. of sulphaphenazole (mg/ml)
10.5	0.02	25
30	0.09	125
60	0.23	325
99	0.27	385
121	0.28	400

To compare the oral absorption of sulphaphenazole and that of acetyl sulphaphenazole, the above results are plotted together in fig 8.

Fig. 8 Plasma conc. of sulphaphenazole vs. time after oral administration of drug.



D I S C U S S I O N

The colorimetric method of sulphcetamide analysis employed in the present work is the most frequently used method for sulphonamide assay (4). This method suffers from lack of specificity because it will react with all aryl amines and sometimes with primary and secondary amines to yield diazotization products and coloured addition compounds which interfere with the assay. This shortcoming is of no great significance in the present investigation because the error if any is standardised. High-pressure liquid chromatography is a more sensitive and specific method than the frequently used colorimetric methods.

Fig 3 shows the absorption of sulphacetamide through five different routes. The area under the curve for each route is a measure of quantity of drug absorbed in to the bloodstream and can be used to compare the efficiency of absorption through the various routes. Intravenous administration is most efficient because drug is injected directly in to the blood-stream. Absorption from both intraperitoneal and intramuscular routes was very rapid and their absorption efficiency is comparable to that of intravenousroute. Both subcutaneous and oral routes gave relatively low plasma level of sulphacetamide. From the graph, the absorption efficiency after 2 hours is iv> ip >im >sc >oral.

From fig 4, it is apparent that acetylation increases the bioavailability of sulphacetamide. Either, acetylation enhances the absorption of sulphacetamide across the gastro intestinal tract barrier in to the bloodstream or the absorbed acetyl sulphacetamide has a higher degree of protein binding such that it is not rapidly excreted.

Fig 5 compares the plasma clearance of both sulphacetamide and acetyl sulphacetamide. The results show that the plasma clearance of sulphacetamide is higher than that of acetyl sulphacetamide. The difference, however, is very small.

This may be as a result of several factors. On one hand, the acetyl sulphacetamide exhibits higher protein binding than sulphacetamide. The protein bound drug is unavailable for excretion. This factor favours a low plasma clearance. On the other hand, the free drug is filtered through the glomeruli and is then partially reabsorbed. The acetyl derivativ is also filtered but is apparently not reabsorbed. This factor favours renal clearance of acetyl sulphacetamide. The observed clearance is a compromise situation between these two factors.

Orally administered sulphaphenrzole is well absorbed from the gastro intestinal tract. Acetyl sulphaphenazole is also well absorbed but not as readily as sulphaphenazole (fig 8). The absorption curves for both sulphaphenazole and acetyl sulphaphenazole do not reach the concentration drop phase within 2 hours. Unlike sulphacetamide, high and steady concentrations are maintained for a relatively long time. Sulphaphenazole is therefore a long acting sulphenamide. Thi long duration of action may be due to the fact that 80% or more of sulphaphenazole in plasma is bound to plasma albumin (8). It is therefore not readily filtered in the gromeruli. Its long duration of action is advantageous in the convenien of administration, but disadvantageous when toxicity occurs. It is especially prone to cause the serious Stevens - Johnson Syndrome (17).

C O N C L U S I O N

From the present work, it has been learned that sulphacetamide produces inadequate plasma levels when administered orally. Hence, an oral dosage form of this drug would be of limited systemic usefulness. This poor bioavailability of sulphacetamide may be due to either of the following reasons:-

(i) It may be well absorbed from the gastro intestinal tract but rapidly excreted due to rapid filtration in the glomeruli coupled with limited reabsorption in the renal tubules. Under such circumstances, it would be a useful agent in the treatment of urinary tract infections (15).

(ii) It may be poorly absorbed from the gastro intestinal tract in which case it would exert a more pronounced effect on the bowel flora.

It is realised that (i) cannot be a possible explanation because the curve for intravenously administered drug shows a more gradual decrease in plasma level of sulphacetamide than would be expected if the explanation was valid. It is therefore concluded that the limiting factor in the bioavailability of orally administered sulphacetamide is its absorption from the gastro intestinal tract (fig. 3).

Acetylation slightly improves bioavailability probably due to an increase in the degree of plasma protein binding when the acetyl derivative is administered (fig. 4).

On the other hand, sulphaphenazole is well absorbed from the gastro intestinal tract. It is therefore useful in treatment of systemic infections caused by susceptible micro-organisms where a high concentration of sulphonamide is required to be maintained in the blood for a reasonably long time. Acetylation slightly reduces rate of sulphaphenazole absorbtion although the same maximum plasma concentration is achieved with either sulphaphenazole or its acetyl derivative. However, acetylation does not appreciably alter the bioavailability of sulphaphenazole (fig.8).

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