# PHARMACOKINETIC STUDY ON INTRAVENOUS RIFAMPICIN IN MAN

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SUMMARY

A pharmacokinetic study was carried out in 18 male patients in order to assess the blood concentrations of rifampicin after intravenous administration of 3 different doses (600, 900 and 1200 mg) over 3 different periods of infusion (1, 2 and 3 hours).

The results show that, by increasing the dose and the rate of infusion higher and earlier peak concentrations are obtained.

A kinetic analysis based on a one-compartment open model gives a good fitting of the data obtained experimentally.

From these data one obtains for the volume of distribution a value of $48.1 \pm 17.2$ liters and for the serum disappearance rate the value of $0.212 \pm 0.070 \ h^{-1}$ in adult subjects.

It is possible to predict the time course of serum kinetics of the drug by using the equation

$$C(t) = \frac{k_o}{20} \ (1 - e^{-0.21 \ t})$$

($t$ = hours, $k_o$ = infusion rate in mg $h^{-1}$).

Introduction

Previous studies have been carried out to assess the time course of
the serum levels of rifampicin (RAMP) in man during and after admi-
nistration of doses ranging from 150 to 600 mg by intravenous infu-
sion (Acocella G. et al., 1977; Nitti V. et al., 1977).

Of the three main variables characterizing an i.v. infusion, namely
the dose, the volume of solution to be injected, and the duration of
infusion, only one was changed in such studies (the dose), the other
two remaining constant (volume = 500 ml and duration of infusion =
3 hours).

Under these experimental conditions the results indicated that there
is a good similarity between the serum concentrations obtained after
administration of the same dose by the oral and the intravenous route,
a fact which indicated the high degree of absorption of rifampicin
from the gastro-intestinal tract.

The present study was undertaken in order to evaluate the pharmaco-
kinetics of RAMP when two of the three variables were modified, namely
the dose and the duration of infusion, keeping the volume of the so-
lution constant.


Material and Methods

1) Subjects. The study was carried out on a group of 18 male patients
   not suffering from diseases or syndromes known or likely to alter
   the kinetics of the antibiotic and who could benefit from the admi-
   nistration of rifampicin. Informed consent was obtained from eve-
   ry patient. Each patient received one infusion according to the
   scheme described below.

2) Treatment. Lyophilized RAMP (300 mg and 600 mg vials) was dissolved
   in the appropriate solvent (5 ml and 10 ml respectively) and added
   to a 500 ml of 5% glucose solution for phleboclysis.
   A dose of 600, 900, and 1200 mg was used.

3) Administration scheme. As said in the introduction, two variables
were modified, the dose and the rate of infusion.   The dose levels
tested were 600, 900 and 1200 mg, each dose being administered in a
constant volume in 3 hours, 2 hours and 1 hour.

| Dose (mg) | Duration of infusion (h) |
|---|---|
| 600 | 3 |
| 600 | 2 |
| 600 | 1 |
| 900 | 3 |
| 900 | 2 |
| 900 | 1 |
| 1200 | 3 |
| 1200 | 2 |
| 1200 | 1 |

Each treatment was administered to 2 patients and each patient recei-
ved a single infusion in order to get serum concentration curves un-
affected by possible changes due to effects of self-induction (Aco-
cella G., Mattiussi R., Segre G., 1978).

In all cases, the infusion was carried out without the aid of arti-
ficial means of constant administration (constant infusion pump).

4) Method of assay.  Rifampicin concentrations were assayed in serum
with the agar-plate method using Sarcina lutea ATCC 9341 as test
microorganism (Furesz S. et al., 1977).

5) Kinetic analysis.  For each patient and scheme of administration
a comparison was carried out between the experimental serum con-
centration data and those calculated according to the equation
reported below.

For each patient the parameters of one-compartment open model were
determined from the observed concentrations, with a constant rate
of entry of the antibiotic in blood ($k_o$) which was known and was de-
pending on the administration scheme.   On the basis of these para-

meters, a fitting of the experimental data was performed for each

case.

The blood samples were taken at time 0, and then at 10; 30; 60; 90

minutes, and 2; 4; 8 hours from the beginning of the infusion.

The mathematical model is

$$dC/dt = -K\,C + k_o/V \qquad \text{for } 0 \leqslant t \leqslant T \text{ (during the infusion)}$$

$$dC/dt = -K\,C \qquad\qquad \text{for} \qquad t > T \text{ (after the infusion)}$$

(C = serum concentration of RAMP ($\mu$g:ml); t = time in hours; T = infu-

sion time; V = volume of distribution in ml; K = elimination constant;

$k_o$ = Dose/T = infusion rate, in mg $h^{-1}$).

The solution of this model is given by the equations:

$$C = \frac{k_o}{V.K}\,(1 - e^{-Kt}) \quad \text{for} \quad 0 \leqslant t \leqslant T \qquad (I)$$

and

$$C = \frac{k_o}{V.K}\,(1 - e^{-KT})\,e^{-K(t-T)} = C(T)\,e^{-K(t-T)} \quad \text{for } t > T \quad (II)$$

The asymptotic value of C can be calculated to be:

$$C(\infty) = \frac{k_o}{V.K} \qquad (III)$$

in this case (when the infusion is carried out for an enough long time)

a steady  state is reached from which one obtains

$$k_o = C(\infty).V.K \qquad (IV)$$

The value of V can be calculated from eq. (IV), being $V = \dfrac{k_o}{C(\infty).K}$, or

from the equation $\dfrac{\text{Dose}}{\displaystyle\int_0^\infty C.dt}$ = Clearance, by noting that: Clearance =

V.K.

The experimental data were fitted to the model by using digital computing

techiniques and the SAAM-27 program (Berman M.,Weiss M.F., 1974).

6. <u>Tolerance</u>. In all patients local tolerance to the infusion was evaluated.

In addition minimal and maximal blood pressure was recorded before, on

completion, and 2 hours after the end of the infusion.

Total serum bilirubin levels were assessed in the same blood sample drawn

for antibiotic assay.

## RESULTS

### Kinetics of rifampicin in blood.

Table I reports the serum concentrations observed at the indicated time in-

tervals with the 9 different administration schemes in 18 subjects.

Within each group, if the rate of infusion is increased, an increase of the

peak values is observed when the highest dose was infused for 1 hour.

In Table II the values of the parameters calculated for each subject are

shown, the mean value of K (elimination constant) is $0.212 \ h^{-1}$ (with a

mean half-life of 3.27 hours) and that of V (volume of distribution)  is

48.14 L; their coefficient of variation is 32.8% and 35.7% respectively.

The value of K does not appear the change noticeably for different doses

or duration of the infusion.

The mean value of K corresponds to the sum of the outflow transfer con-

stants from the central compartment obtained in a previous study (Aco-

cella G., Mattiussi R., Segre G., 1978) of serum kinetics of RAMP after

oral administration from which the value of $0.236 \ h^{-1}$  is obtained and

which is mainly due to the biotransformation of RAMP into desacetyl-RAMP

$(0.221 \ \underline{+} \ 0.090 \ h^{-1})$.

The values of AUC $\int_{o}^{\infty}$  C.dt calculated by the trapezoidal method are

shown in Table III.

It is evident that the values of AUC for the 2 cases in which 1200 mg

of RAMP were infused in 1 hour are quite erratic with respect to the other

cases in which the same dose was infused at a slower rate.

It can be assumed that in these 2 cases the kinetics approaches a satura-

tion phenomenon.

TABLE I - SERUM RIFAMPICIN LEVELS (μg/ml) OBSERVED AT THE INDICATED TIME INTERVALS DURING AND AFTER AN I.V. INFUSION OF DIFFERENT DOSES OVER DIFFERENT INFUSION TIMES

| DOSE (mg) | DURATION OF THE INFUSION (hours) | SUBJECT No. | SERUM RIFAMPICIN LEVELS AT THE INDICATED TIME FROM THE BEGINNING OF THE INFUSION | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | 10 min | 30 min | 1 h | 1½ h | 2 h | 4 h | 8 h. |
| 600 | 3 | 1 | 0.80 | 2.10 | 3.89 | 5.95 | 7.06 | 6.29 | 2.81 |
| | | 2 | 0.92 | 1.09 | 2.33 | 3.98 | 3.64 | 6.04 | 3.56 |
| 600 | 2 | 3 | 1.12 | 1.87 | 3.39 | 5.96 | 9.39 | 5.73 | 2.24 |
| | | 4 | 1.11 | 1.68 | 1.97 | 3.49 | 6.41 | 1.70 | 0.27 |
| 600 | 1 | 5 | 5.19 | 10.48 | 13.81 | 12.20 | 10.48 | 8.85 | 3.59 |
| | | 6 | 5.71 | 11.99 | 14.92 | 12.05 | 11.48 | 7.48 | 1.54 |
| 900 | 3 | 7 | 1.12 | 2.58 | 4.33 | 6.01 | 6.76 | 6.72 | 3.59 |
| | | 8 | 1.40 | 2.12 | 4.52 | 6.44 | 9.20 | 8.01 | 4.27 |
| 900 | 2 | 9 | 1.31 | 2.47 | 6.19 | 9.55 | 12.84 | 9.82 | 5.14 |
| | | 10 | 4.58 | 8.54 | 11.63 | 16.72 | 16.77 | 8.71 | 3.25 |
| 900 | 1 | 11 | 8.87 | 19.79 | 20.94 | 16.65 | 14.89 | 9.67 | 3.70 |
| | | 12 | 7.28 | 12.93 | 13.87 | 12.99 | 20.09 | 14.58 | 8.37 |
| 1200 | 3 | 13 | 1.60 | 2.81 | 6.92 | 11.70 | 14.32 | 11.76 | 5.25 |
| | | 14 | 5.47 | 7.55 | 14.13 | 17.34 | 22.39 | 17.87 | 11.95 |
| 1200 | 2 | 15 | 2.46 | 4.06 | 9.06 | 12.57 | 13.62 | 8.65 | 4.73 |
| | | 16 | 3.27 | 4.89 | 11.23 | 14.65 | 15.89 | 11.16 | 5.18 |
| 1200 | 1 | 17 | 10.42 | 24.93 | 31.13 | 19.94 | 18.40 | 23.45 | 10.85 |
| | | 18 | 9.52 | 19.91 | 38.42 | 26.63 | 25.02 | 23.57 | 13.27 |

Kinetic parameters computed in 18 subjects

| Subj. No. | $k_o$ (mg h$^{-1}$) | T (h) | Dose (mg) ($k_o T$) | $C(\infty) = \dfrac{k_o}{VK}$ (ug/ml) | K (h$^{-1}$) | V (L) | Cl (Dose/AUC) (ml/h) |
|---|---|---|---|---|---|---|---|
| 1 | 200 | 3 | 600 | 16.48 | 0.25 | 48.54 | 11.76 |
| 2 | 200 | 3 | 600 | 21.20 | 0.155 | 60.86 | 10.05 |
| 3 | 300 | 2 | 600 | 23.41 | 0.19 | 67.41 | 12.07 |
| 4 | 300 | 2 | 600 | 75.11 | 0.38 | 10.51 | 37.26 |
| 5 | 600 | 1 | 600 | 80.47 | 0.21 | 35.50 | 7.58 |
| 6 | 600 | 1 | 600 | 58.82 | 0.34 | 30.00 | 9.90 |
| 7 | 300 | 3 | 900 | 19.47 | 0.22 | 70.09 | 15.17 |
| 8 | 300 | 3 | 900 | 24.27 | 0.20 | 61.85 | 12.38 |
| 9 | 450 | 2 | 900 | 50.96 | 0.125 | 70.09 | 8.51 |
| 10 | 450 | 2 | 900 | 43.41 | 0.27 | 38.39 | 11.51 |
| 11 | 900 | 1 | 900 | 97.00 | 0.24 | 38.66 | 9.65 |
| 12 | 900 | 1 | 900 | 105.00 | 0.20 | 42.86 | 6.19 |
| 13 | 400 | 3 | 1200 | 32.39 | 0.23 | 53.69 | 12.26 |
| 14 | 400 | 3 | 1200 | 61.81 | 0.21 | 30.82 | 5.95 |
| 15 | 600 | 2 | 1200 | 48.73 | 0.175 | 70.67 | 13.27 |
| 16 | 600 | 2 | 1200 | 56.00 | 0.18 | 59.52 | 11.18 |
| 17 | 1200 | 1 | 1200 | 271.00 | 0.10 | 44.28 | 5.18 |
| 18 | 1200 | 1 | 1200 | 252.85 | 0.145 | 32.73 | 4.48 |
| Mean | - | - | - | - | 0.212 | 48.137 | 9.93 |
| s.d. | - | - | - | - | 0.0696 | 17.1888 | 3.078 |

TABLE III

Values of the $AUC_o^8$ (mg/ml/h) for the various doses and

durations of infusion of rifampicin.

| Dose (mg) | Duration of infusion (h) 1 | 2 | 3 | mean AUC + s.d. |
|-----------|------|------|------|-----------------|
| 600       | 79.1 | 49.7 | 51.0 | 52.70 + 20.78   |
|           | 60.6 | 16.1 | 59.7 |                 |
| 900       | 93.3 | 105.7| 5S.3 | 92.43 + 30.57   |
|           | 145.4| 79.2 | 72.7 |                 |
| 1200      | 231.4* | 90.4 | 97.8 | 166.08 + 77.13 |
|           | 267.9* | 107.3 | 201.7 | 124.30 + 52.06** |

** value calculated omitting *

Fig. 1 - Plot of $k_0$ vs C (∞)
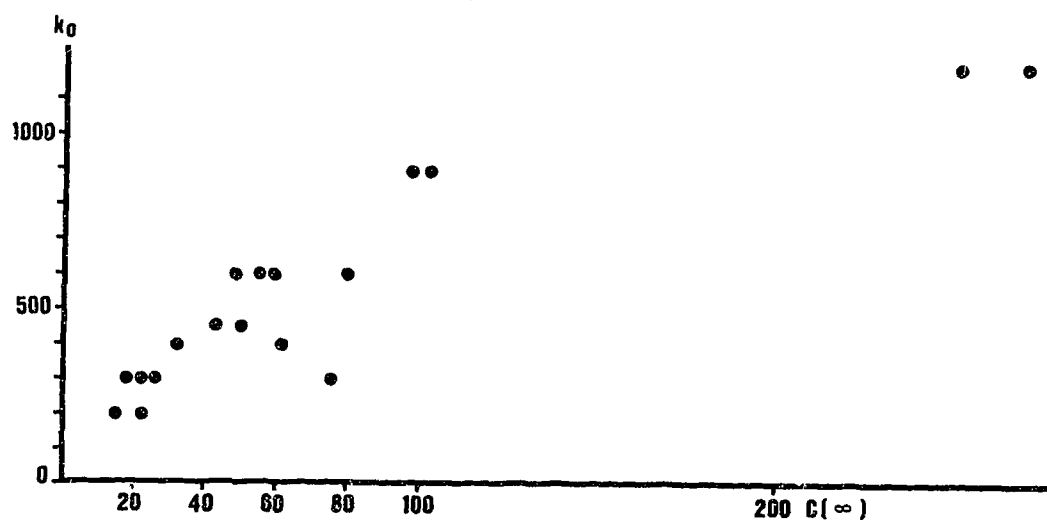


If these 2 cases are excluded one obtains for the regression between

AUC (y) and the dose (x) the equation:

$$y = -18.27 + 0.120 \ x \quad (r = 0.677; \ P < 0.01).$$

The values of the total body clearance calculated from the formula: dose/

AUC are shown in Table II; their mean value is equal to about 10 ml/h.

A plot of $k_o$ vs C ($\infty$ ) (see Tab. II) shows (fig. 1) that, if the two

values of C ($\infty$ ) for $k_o$ equal to 1200 are eliminated, the other values

can fit a  straight line:

$$C (\infty) = 0.185 + 0.108 . k_o \quad (r = 0.844; P < 0.001)$$

whereas the previous two values  are not along the straight line; therefore

it appears that at an infusion rate of 1200 mg $h^{-1}$ the elimination pro-

cess is no more linear;  in fact at a closer examination of the serum

kinetics of these two subjects (No. 17 and 18)  it is difficult to ascer-

tain whether it follows a zero or a first order.


Tolerance

For all the administration schemes investigated the local tolerance was

entirely satisfactory.

The serum total bilirubin levels are reported in Table IV.

As expected on the basis of the interaction between RAMP and bilirubin

which compete with each other for biliary excretion (Acocella G., Mat-

tiussi R., Tenconi L.T., 1973), a certain increase of the serum bili-

rubin levels was observed.

As a result  of competition, RAMP is preferentially excreted, this slow-

ing down the transfer of bilirubin through the liver;  in consequence the

serum total bilirubin concentrations increase.

The increase was of little, if any, relevance in the subjects receiving

the 600 mg dose and the 900 mg dose in three hours, the levels being in

these cases within the normal range.

Levels somewhat higher than the upper limit of normality (1 mg/100 ml

serum) were found to be associated with the administration of 900 mg in

1 hour and of 1200 mg in 2 and 1 hour.

In agreement with previous data on i.v. infusion of rifamycin  SV (Aco-

cella G., Nicolis F.B.,Tenconi L.T., 1965) the phenomenon was more marked

at the higher rate of administration.

With rifamycin SV and rifamycin M14 (Acocella G., Nicolis F.B., Tenconi

TABLE IV

Serum bilirubin levels (mg/100 ml) at different time intervals during and after an i.v. infusion of rifampicin at different doses over a different period of infusion.

| DOSE (MG) | DURATION OF THE INFUSION (HOURS) | SUBJECT No. | SERUM BILIRUBIN LEVELS | | | |
|---|---|---|---|---|---|---|
| | | | 0 | 2 H | 4 H | 8 H |
| 600 | 3 | 1 | 0.38 | 0.54 | 0.70 | 0.86 |
| | | 2 | 0.36 | 0.65 | 0.81 | 0.54 |
| 600 | 2 | 3 | 0.59 | 0.73 | 0.62 | 0.54 |
| | | 4 | 0.22 | 0.59 | 0.43 | 0.32 |
| 600 | 1 | 5 | 0.48 | 0.54 | 0.65 | 0.58 |
| | | 6 | 0.38 | 0.65 | 0.54 | 0.36 |
| 900 | 3 | 7 | 0.43 | 0.59 | 0.97 | 0.81 |
| | | 8 | 0.36 | 0.65 | 0.78 | 0.48 |
| 900 | 2 | 9 | 0.22 | 0.65 | 0.76 | 0.58 |
| | | 10 | 0.59 | 0.97 | 1.41 | 1.03 |
| 900 | 1 | 11 | 0.28 | 0.97 | 0.76 | 0.65 |
| | | 12 | 0.54 | 0.81 | 0.97 | 0.75 |
| 1200 | 3 | 13 | 0.54 | 0.65 | 0.83 | 0.65 |
| | | 14 | 0.32 | 0.76 | 0.97 | 0.92 |
| 1200 | 2 | 15 | 0.36 | 0.97 | 1.14 | 1.03 |
| | | 16 | 0.54 | 0.76 | 0.97 | 0.75 |
| 1200 | 1 | 17 | 0.28 | 1.28 | 1.10 | 0.76 |
| | | 18 | 0.36 | 0.88 | 0.99 | 1.08 |

L.T., 1965; Acocella G. et al., 1966) and with oral rifampicin (Acocella G., Mattiussi R., Tenconi L.T., 1973) the increase was found to be transient, the bilirubin levels returning within normal limits a few hours after stopping the infusion.

The comparison of the 8th versus 4th hours values and the levels at the 12th hour in subjects No. 17 and 18, strongly suggests that a similar situation occurs with i.v. RAMP.

TABLE  V - MAXIMAL AND MINIMAL BLOOD PRESSURE VALUES RECORDED AT THE BEGINNING, AT THE END AND

2 HOURS AFTER THE END OF THE INFUSION OF DIFFERENT DOSES OF RIFAMPICIN

| DOSE (MG) | DURATION OF THE INFUSION (HOURS) | SUBJECT No. | MAXIMAL AND MINIMAL BLOOD PRESSURE | | |
|---|---|---|---|---|---|
| | | | 0 | END OF THE INFUSION | 2 H AFTER THE END OF THE INFUSION |
| 600 | 3 | 1 | 145/85 | 140/80 | 145/90 |
| | | 2 | 105/80 | 100/75 | 100/75 |
| 600 | 2 | 3 | 135/60 | 145/70 | 135/70 |
| | | 4 | 115/50 | 105/55 | 115/60 |
| 600 | 1 | 5 | 160/85 | 145/90 | 160/95 |
| | | 6 | 115/75 | 115/70 | 115/70 |
| 900 | 3 | 7 | 130/90 | 120/80 | 120/80 |
| | | 8 | 130/70 | 135/80 | 125/70 |
| 900 | 2 | 9 | 110/60 | 105/70 | 100/60 |
| | | 10 | 115/80 | 125/80 | 125/90 |
| 900 | 1 | 11 | 140/70 | 130/80 | 145/80 |
| | | 12 | 140/85 | 150/100 | 150/95 |
| 1200 | 3 | 13 | 120/80 | 130/80 | 130/80 |
| | | 14 | 150/80 | 145/95 | 140/85 |
| 1200 | 2 | 15 | 140/80 | 120/80 | 140/80 |
| | | 16 | 105/55 | 120/70 | 100/70 |
| 1200 | 1 | 17 | 115/75 | 105/75 | 120/80 |
| | | 18 | 140/80 | 140/70 | 150/90 |

The values of arterial blood  pressure recorded before, on completion

and 2 hours after the end of the infusion have shown a slight increase or

decrease in the values which seem compatible with the normal variation

inherent in the measurement process (+ 10 mm Hg) (Table V ).


DISCUSSION AND CONCLUSIONS

The results of the present study indicate that by increasing the dose of

rifampicin from 600 to 1200 mg and by reducing the duration of infusion

from 3 to 1 hour at constant volume a linear  increase in serum asymptotic

concentration, C ($\infty$), is obtained for infusion rates from 200 to 900 mg h$^{-1}$.

Above this rate (at 1200 mg h$^{-1}$), the values of C ($\infty$) show a departure from linearity; this fact points to a saturation kinetics in the elimination process when serum levels of RAMP reach and exceed a given value (between 25 and 30 ug/ml).

For the same range of administration schemes, a close correspondence between the experimental curve and that calculated on the basis of a one-compartment open model was found.

The kinetic analysis has provided evidence that the numerical value of the sum of the 3 basic transfer constants governing the process of disposal of rifampicin from the human body is similar when calculated for the oral and for the i.v. administration (Acocella G., Mattiussi R. and Segre G., 1978).

This result is of particular relevance since the two conditions are remarkably different, the first involving the existence of a very important (for rifampicin) first-pass effect through the liver; whereas the second implies by definition a by-passing of the liver, the drug entering directly the central (blood) compartment.

Further studies are needed to clarify the mechanism underlying the saturation process which appers to operate at high levels of rifampicin.

A comparative study on the biliary excretion of the drug in various conditions of administration could probably help in solving the problem.

From the clinical viewpoint and having in mind the proposed conditions of use, the kinetic properties of i.v. rifampicin seem particularly encouraging. The "predictability" of the magnitude of the peak concentration for a given rate of infusion seems a particularly useful feature if one has in mind the treatment of severe cases where, for example, oral administration of drug can be a problem.

In addition, the possibility of predicting with a reasonable approximation the serum kinetics for different infusion rates in a given patient will allow the attending physician to select the most appropriate administration scheme capable of keeping under control an infectious process caused

by a microorganism whose sensitivity to rifampicin has been assessed.

By using the equation (I) and the mean values for K and for the product K.V obtained from Table II one gets

$$C(t) = \frac{k_o}{20} \ (1 - e^{-0.21t}).\qquad\qquad (V)$$

By substituting $k_o$ with the real value (until 900 mg) one can approximate the expected mean time-course of serum concentrations of rifampicin during the infusion.

By using equation (V) one obtains for C(t) values somewhat higher than those found experimentally in Table I for lower values of $k_o$ (200 and 300 ) and values somewhat lower for higher values of $k_o$ for an infusion of 2 hours.

It should however be observed that the variability of the experimental data (calculated for $k_o$ = 300, for which value 4 experiments are availble) corresponds to a coefficient of variation of about 22%.

However the better imput (in order to achieve immediately and maintain serum levels of about 10 mcg/ml) should be a priming i.v. dose of 0.5 g of rifampicin and infuse at the same time the drug at a rate $(k_o)$ of 100 mg $h^{-1}$ .

Since rifampicin administered by oral route shows a good bioavailability and since the transfer from the G.I. tract to circulatory blood requires one step only (Acocella G., Mattiussi R., Segre G., 1978), no differences of relevance between serum levels after oral and i.v. administration of the same dose are observed.

A further element in common between the oral and the i.v. use of rifampicin is that of the interaction between the drug and the liver which was very much in agreement with what we expected on the basis of the present knowledge on rifamycins.

In conclusion, the intravenous infusion seems to be a well-tolerated way of administering rifampicin, which generates predictable serum levels. In some respect, as with other antibiotics, the i.v. route seems to

present some advantage in comparison to the oral route, a fact which can

find its most useful application in selected clinical cases.

REFERENCES

1) ACOCELLA G., NICOLIS F.B., and TENCONI L.T. (1965). Gastroenterology
   49, 521-25

2) ACOCELLA G. et al. (1966). Gut 7, 380-86.

3) ACOCELLA G., MATTIUSSI R., and TENCONI L.T. (1973). Tijdschrift voor
   Gastro-Enterologie 16, 186-190.

4) ACOCELLA G. et al. (1977). Arzneimittel-Forschung 27, 1221-26.

5) ACOCELLA G., MATTIUSSI R., and SEGRE G. (1978). Pharmacological
   Research Communications 10, 271-88.

6) BERMAN M., WEISS M.F. (1974). SAAM 27 Manual, Laboratory of Theore-
   tical Biology, National Cancer Institute, National Institute of
   Health, Bethesda, Maryland.

7) FURESZ S. et al. (1977). Arzneimittel-Forschung 17, 726-35.

8) NITTI V. et al. (1977). Chemotherapy 23, 1-6.