The Relationship Between the Metabolism of Procainamide and Sulfamethazine

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SUMMARY The metabolism of sulfamethazine (SMZ), which is acetylated by a bimodally distributed enzyme, and procainamide (PA) was compared in 21 normal volunteers, each given a single oral dose of SMZ and PA (10 mg/kg). Urinary PA and SMZ concentrations and acetylated metabolites, N-acetyl-procainamide (NAPA) and Ac-SMZ, were measured. Subjects with less than 64% Ac-SMZ in the 0–8 hour collection were termed "slow" and those with more than 64% were termed "fast" SMZ acetylators. Slow SMZ acetylators had 9.8 to 43.8% (24.1 ± 10.13) NAPA recovered, and fast SMZ acetylators, 22.0 to 42.6% (33.7 ± 7.29) NAPA, P < 0.01. In addition, the calculated half-life of PA metabolism for slow SMZ acetylators was 9.0 to 33.8 hours (18.4 ± 8.82) and for fast SMZ acetylators was 8.1 to 14.4 hours (10.9 ± 2.19), P < 0.01. For four subjects, SMZ acetylation phenotype did not correlate with the half-life of SMZ or PA metabolism; and in two, SMZ acetylation phenotype and half-life of metabolism did not correlate with the same PA indices. Even though slow SMZ acetylators have less NAPA recovered than fast SMZ acetylators, it is not yet clear that procainamide is metabolized by a bimodally distributed enzyme as is sulfamethazine.

Since Dreyfuss et al. reported that procainamide (PA) is metabolized to N-acetylprocainamide (NAPA),1 the acetylation of PA has been investigated in several laboratories. 2-4 The acetylation of PA has been suggested to be under the control of the hepatic N-acetyltransferase enzyme which has a bimodal distribution in the human population5-7 rather than by the acetylases with a unimodal distribution. The bimodally distributed enzyme accounts for the acetylation of isoniazid (INH),7 sulfamethazine (SMZ)6,8 and dapsone9 whereas the unimodally distributed enzyme accounts for the acetylation of para-aminobenzoic acid,7 para-aminosalicylic acid10 and sulphanilamide.6

A number of investigators4-8 have observed a relationship between the fraction of NAPA and the PA dose recovered and the acetylation phenotype determined with INH or dapsone in normal volunteers6-8 or cardiac subjects.4 Slow INH or dapsone acetylators have been reported to slow PA acetylators, based on the fraction of NAPA recovered in timed urine4, 8 and plasma4 samples following a dose of PA. However, acetylation phenotype determined from the fraction of NAPA recovered in a timed urine or plasma sample has limitations. For example, a subject who is a phenotypic slow acetylator but has a prolonged rate of renal excretion due to congestive heart failure or renal disease can excrete a larger fraction of PA as NAPA because more time is available for hepatic metabolism. Therefore, the NAPA/ NAPA + PA ratio could be an inaccurate estimate of acetylation phenotype even when all of a PA dose is accounted for.

This study was initiated in order to determine the relationship between the acetylation phenotype of normal volunteers given sulfamethazine (SMZ), a drug metabolized by the bimodally distributed polymorphic acetylace, and the extent and rate of PA acetylation. Determination of the acetylation phenotype was based on the amount of acetylated SMZ (Ac-SMZ) in an 8 hour collection.9 The criteria for classifying an individual as a fast or slow SMZ acetylator from the fraction, Ac-SMZ/PA-SMZ + SMZ, collected in the urine collected for eight hours after an oral dose was based on the data from 119 subjects reported by White and Price-Evans.9 That is, subjects who had 64% or less of Ac-SMZ* in urine collected for eight hours were termed slow SMZ acetylators and those who had more than 64% were termed fast SMZ acetylators. The figure, 64%, was derived from the relative minimum between the two modes of a frequency histogram in which the acetylation of SMZ was shown to have a bimodal distribution.8 Then the calculated half-life of SMZ and PA metabolism were compared in normal volunteers. Thus, our study was designed to provide further insight into the kinetics of the metabolism of PA by comparing the amount of NAPA recovered to that of Ac-SMZ and by comparing the half-life of PA metabolism to the half-life of SMZ metabolism.

Methods and Materials

Twenty-one normal volunteers (table 1) gave their informed, written consent to take a single oral dose of PA and SMZ. Prior to administering the dose, a medical history and physical examination, CBC, urinalysis, blood sugar, creatinine clearance and liver function tests were measured in all volunteers. After an overnight fast, each volunteer took 10 mg/kg of either SMZ or PA; the second drug was given after an interval of at least 10 days. The sequence of the medications was assigned in random order. Urine samples for SMZ concentration were collected at 0–2, 2–4, 4–6, 6–8, 8–10, 10–12, 12–24, 24–28, 28–32 and 32–36 hours after a dose and urine samples for PA concentration were

\[
\text{Ac-SMZ} \times 100 \text{ in 0–8 hour urine sample}
\]

\[
\text{Ac-SMZ} + \text{SMZ (mg)}
\]
collected at 0–2, 2–4, 4–6, 6–8, 8–10, 10–12 and 12–24 hours after a dose.

Procainamide in urine was determined by the method of Mark et al. Samples of urine were extracted into benzene, returned to hydrochloric acid, reacted with Bratton-Marshall reagents, and read in the spectrophotometer at 550 nm. Procainamide concentrations were expressed as \( \mu g/ml \) base. For determination of NAPA, plasma was extracted as described for PA, hydrolyzed with a final concentration of 2N HCl for one hour at 100°C, reacted with the Bratton-Marshall reagents, and absorbance was measured as for PA. This method measures the acetylated metabolite of PA, i.e., NAPA, but probably not any metabolites of PA which are not acetylated. Duplicate samples of PA and NAPA were reproducible within 3%. Free and total SMZ concentration in urine were determined in an analogous way by the Bratton-Marshall procedure.

To compare concentrations of PA and NAPA measured by spectrophotometry with gas chromatographic measurements, urine samples of ten subjects were selected randomly and analyzed by a gas chromatographic method. One ml of diluted urine was placed in a tube to which was added 1 ml of an internal standard (the dipropyl analog of procainamide, p-amino-N-[2-dipropyl-aminoethyl]-benzamide HCl [melting point = 188–190°C]), 0.4 ml of 2.5 Normal NaOH and 5 ml of methylene chloride. (NAPA and the internal standard were supplied by the Squibb Institute for Medical Research.) The mixture was shaken, centrifuged and the methylene chloride layer removed, evaporated, and the residue dissolved in 40 \( \mu l \) of ethyl acetate and 1.5–2.0 \( \mu l \) was injected into the gas chromatograph (Hewlett-Packard 7620A). The column was a small-bore glass column (6 ft \( \times \) 1 mm) and packed with 3% OV-17 liquid phase on a solid support of Chromosorb W-HP. For PA analysis, the temperature of the oven was 240°C, detector and injection port was 255°C; for NAPA analysis the oven temperature was 250°C and injection port and detector were 265°C. Nitrogen at a flow rate of 40 ml/min was used as the carrier gas. The retention times for PA and NAPA were 6 and 20 min at an oven temperature of 240°C and 250°C, respectively. The retention time for the internal standard varied between 7.6 and 8 min at oven temperatures of 240°C and 250°C. For each subject a standard curve for PA over a range of 10–20 \( \mu g/ml \) was determined and a standard curve for NAPA of 15–30 \( \mu g/ml \) was determined. Urine samples were diluted into the range of the standard curve. Duplicate samples were reproducible within 5%.

The rate constants for elimination, metabolism, and excretion of PA and SMZ were calculated as described below. The rate method used to determine the rate constant for elimination into urine is illustrated in figure 1. This method was selected since 1) it avoids very frequent blood samples, 2) collection of urine over 6–7 half lives is not necessary, and 3) the loss of one urine specimen does not invalidate the entire experiment. Some of these problems are inherent in the sigma minus method. The calculations were done as follows:

A) \( k_{el} \) was calculated from the excretion rate of PA (or SMZ) versus time plot, using the urinary data in its linear log phase, up to 24 hours for PA and 36 hours for SMZ. In the 20 volunteers, the correlation coefficient for the terminal slope of PA ranged between \( r = 0.78 \) and 0.96 (0.87 \( \pm \) 0.05 : mean \( \pm \) SD) and for SMZ ranged between \( r = 0.74 \) and 0.92 (0.84 \( \pm \) 0.04). \( t\frac{1}{2} \) of PA (or SMZ) elimination was calculated as

\[
\frac{0.693}{k_{el}}
\]

B) \( k_{ex} = k_{el} \times \text{PA (or SMZ) recovered in 24 (or 36) hr} \)

Total dose PA (or SMZ) in 24 (or 36) hr

\( t\frac{1}{2} \) of PA (or SMZ) renal excretion was calculated as

\[
\frac{0.693}{k_{ex}}
\]

where the drugs were measured in mg recovered in urine

C) \( k_{m} = k_{el} - k_{ex} \)

\( t\frac{1}{2} \) of PA (or SMZ) metabolism was calculated as

\[
\frac{0.693}{k_{m}}
\]

where \( k_{ex} \) = rate constant for the elimination of the drug; \( k_{ex} \) = rate constant governing urinary excretion of unchanged drug; and \( k_{m} \) = rate constant for formation of all metabolites

\[
(k_{m} = k_{m1} + k_{m2} + \ldots)
\]

Results

SMZ Metabolism

In the 21 subjects, from 44 to 97% (69.9 \( \pm \) 8.51) of the SMZ dose recovered in the 0–8 hour urine was Ac-SMZ (table 1). Nine subjects who had from 44 to 64% (57.4 \( \pm \) 6.23) of the dose recovered as Ac-SMZ were classified as slow acetylators of SMZ and the 12 subjects who had from 65.6 to 97% (79.3 \( \pm \) 10.80) recovered as Ac-
SMZ were classified as fast acetylators of SMZ according to the method of White and Price-Evans. The t½ of elimination for SMZ in all 21 subjects ranged from 6.1 to 13.6 hours (9.7 ± 2.05) and was not significantly different for the slow and fast SMZ acetylators. The half-life of metabolism for SMZ calculated for all subjects ranged from 7.7 to 19.7 hours (13.5 ± 3.0) (table 2); for the slow SMZ acetylators it ranged from 11.4 to 19.7 hours (15.3 ± 2.99) and for the fast SMZ acetylators it ranged from 7.7 to 17.4 hours (11.7 ± 3.06) (P < 0.05). Two of the subjects, A.W. and R.W., who were classified as fast SMZ acetylators, by the criteria of White and Price-Evans, each had a half-life of metabolism for SMZ which was quite long, i.e., 17.4 and 14.4 hours, respectively, considerably longer than the average half-life of metabolism for SMZ for the fast acetylators (11.7 ± 3.06 hours). Two other subjects, L.B. and R.L., who had been typed as slow SMZ acetylators each had half-lives of metabolism for SMZ of 13.1 hours and 11.4 hours, both relatively fast when compared to the mean of 15.3 ± 2.99 hours for the rest of the slow SMZ acetylators. The latter four subjects probably represent classification errors of the method of White and Price-Evans; no obvious source for error in the estimation of their half-lives could be found. Each strictly adhered to the protocol, each had good total recovery of the SMZ dose, mean of 92 ± 7.1%, and the mean correlation coefficient for k_to was 0.87 ± 0.03.

**Procainamide Metabolism**

There is a linear relationship between the percent of Ac-SMZ recovered in 8 hours and the percent of NAPA recovered in 24 hours after a dose (r = 0.66) (fig. 2). The fraction of the PA dose acetylated in each subject was considerably less than the fraction of SMZ dose acetylated. Nevertheless, for the majority of the subjects acetylation of PA was consistent with that of SMZ. When subjects were ranked from one to 21 for percent Ac-SMZ recovered in 8

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*Student's t-test between means

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1 NAPA (mg) = \( \times 100 \) in 0-24 hour urine sample

NAPA + PA (mg)
hours and compared to percent NAPA recovered in 24 hours, the rank correlation coefficient was $r = 0.65$. For the 21 subjects from 9.8 to 43.8% (28.9 ± 8.5) NAPA was recovered in the urine (table 1) in 24 hours. The percent of NAPA recovered for the slow SMZ acetylators ranged from 9.8 to 43.8% (24.1 ± 10.13) and for the fast SMZ acetylators ranged from 22 to 42.6% (33.7 ± 7.29) ($P < 0.01$).†

The half-life of elimination for PA ranged from 3.0 to 4.8 hours (3.6 ± 0.45) and was not significantly different for individuals classified as slow or fast SMZ acetylators by the method of White and Price-Evans (table 3). The half-life of metabolism for PA was significantly different for the slow SMZ acetylators: 9.0 to 33.8 hours (18.4 ± 8.82) as compared to 8.1 to 14.4 hours (10.9 ± 2.19) for fast SMZ acetylators ($P < 0.01$).† A linear regression comparing the relationship between half-life of metabolism for SMZ with PA had a correlation coefficient of 0.47.

In the four subjects who probably represent misclassification of phenotype by the method of White and Price-Evans the acetylation phenotype determined from SMZ did not correlate with either the half-life of metabolism for SMZ or for PA. A.W. and R.W., who had been classified as fast SMZ acetylators, each had a long half-life of SMZ metabolism, and also had a relatively long half-life of PA metabolism — 13.9 and 13.1 hours each — longer than the mean half-life of metabolism of PA for the other fast SMZ acetylators, 10.9 ± 2.19 hours. L.B. and R.L., who had been typed as slow SMZ acetylators, each had a relatively short half-life of metabolism for SMZ, and had a half-life of metabolism for PA calculated to be 12.9 hours and 12.8 hours — relatively short compared to the mean half-life of metabolism for PA, 18.4 ± 8.82 hours, for the other slow SMZ acetylators.

Two other subjects illustrate another problem, namely, environmental factors which may alter acetylation phenotype from one drug to another. In these individuals neither the SMZ acetylation phenotype nor half-life of metabolism for SMZ corresponded with the fraction recovered in the urine as NAPA or the half-life of metabolism of PA. F.B. had been classified as a slow SMZ acetylator and had a relatively long half-life of metabolism for SMZ (15.0 hours). However, he had 43.8% of NAPA recovered as well as a half-life of metabolism for PA of 9 hours. In contrast, A.S. who had been classified as a fast SMZ acetylator and who had a relatively short half-life of SMZ metabolism (tables 1 and 2) had relatively small quantities of NAPA (22%) recovered and additionally had a long half-life of metabolism for PA (14.4 hours).

### Comparison Between Colorimetric and Gas Chromatographic Analysis

In ten randomly selected subjects, urinary PA and NAPA were measured using both colorimetric and gas chromatographic techniques. In these subjects, the percent of NAPA ($\frac{\text{NAPA}}{\text{PA} + \text{NAPA}} \times 100$) recovered in the urine from 0–24 hours ranged from 22 to 42.6% (30.4 ± 4.85) by colorimetry and 16 to 45% (27.3 ± 6.11) by gas chromatography. The average difference between the two methods was tested by a paired $t$-test and was not significant at the 0.05 level. The correlation coefficient between concentrations determined by the two methods was 0.88.

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†Student's $t$-test between means

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**TABLE 2.** **Half-life of Metabolism, Elimination, and Excretion of SMZ in 21 Subjects**

<table>
<thead>
<tr>
<th>Subject</th>
<th>SMZ Metabolism ($t_{1/2}$ hr)</th>
<th>SMZ Elimination ($t_{1/2}$ hr)</th>
<th>SMZ Excretion ($t_{1/2}$ hr)</th>
<th>SMZ Dose (mg)</th>
<th>SMZ Recovered* (mg)</th>
<th>Ac-SMZ* Recovered (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. MS</td>
<td>13.4</td>
<td>8.3</td>
<td>21.7</td>
<td>830</td>
<td>275.2</td>
<td>446.8</td>
</tr>
<tr>
<td>2. SG</td>
<td>13.4</td>
<td>8.9</td>
<td>24.8</td>
<td>550</td>
<td>153.7</td>
<td>319.7</td>
</tr>
<tr>
<td>3. DR</td>
<td>19.7</td>
<td>12.4</td>
<td>33.0</td>
<td>614</td>
<td>213.4</td>
<td>360.6</td>
</tr>
<tr>
<td>4. RL</td>
<td>11.4</td>
<td>8.0</td>
<td>26.7</td>
<td>709</td>
<td>206.3</td>
<td>495.2</td>
</tr>
<tr>
<td>5. FB</td>
<td>15.0</td>
<td>10.2</td>
<td>31.5</td>
<td>685</td>
<td>203.0</td>
<td>430.9</td>
</tr>
<tr>
<td>6. JB</td>
<td>19.5</td>
<td>13.6</td>
<td>46.2</td>
<td>735</td>
<td>196.5</td>
<td>452.5</td>
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<tr>
<td>7. LB</td>
<td>13.1</td>
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<td>24.8</td>
<td>682</td>
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<td>36.5</td>
<td>904</td>
<td>234.2</td>
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<td>9. RD</td>
<td>17.7</td>
<td>12.4</td>
<td>40.8</td>
<td>815</td>
<td>163.4</td>
<td>385.2</td>
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<tr>
<td>Mean ± SD</td>
<td>15.3 ± 2.99</td>
<td>10.3 ± 2.06</td>
<td>31.8 ± 8.20</td>
<td>723.8 ± 109.49</td>
<td>206.7 ± 33.6</td>
<td>430.7 ± 81.69</td>
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</tbody>
</table>

*SMZ (mg) or Ac-SMZ (mg) recovered in 0-36 hour urine collection.
% SMZ METABOLIZED (8 hours)

Figure 2. A linear regression illustrating the relationship between the percentage of PA metabolized (urine collection of 24 hours) and the percentage of SMZ metabolized (urine collection of 8 hours) (r = 0.66). The vertical line separates "slow" from "fast" SMZ acetylators, according to the criteria of White and Price-Evans. The symbols represent the individuals cited in the text and the open circles represent the remaining 15 subjects.

Discussion

In the four years since the report of the discovery of the major metabolite of procainamide, NAPA, a number of independent investigators have found that from 5 to 55% of a dose of PA is recovered in the urine in normal volunteers and patients recovering from acute myocardial infarction. Marked individual variability in the fraction of PA metabolized has been attributed to a genetically determined acetylation phenotype. Gibson observed that ten fast INH acetylators metabolized PA more rapidly than four slow INH acetylators; Karlsson noted a significant correlation between the plasma INH half-life and the fraction of a dose recovered as NAPA in 15 patients with acute myocardial infarction; and Reidenberg observed that the NAPA/PA ratio in a timed plasma sample was significantly higher in eight rapid dapsone acetylators as compared to six slow dapsone acetylators. These investigators have concluded that PA is acetylated by N-acetyltransferase which is distributed bimodally within the population.

This enzyme metabolizes INH and dapsone while a unimodally-distributed enzyme is responsible for the metabolism of para-amino-salicylic acid and sulfanilamide.

The metabolism of PA is of particular interest because determination of acetylation phenotype may help predict which patients will develop side effects. Procainamide-induced side effects may be more common in slow acetylators. This view is reasoned by analogy from the increased frequency of untoward drug-induced side effects in slow acetylators of drugs metabolized by the enzyme which has a bimodal distribution: hydralazine, phenelzine, and isoniazid. Little evidence has been gathered as yet to indicate that slow acetylators of PA are more prone to the systemic lupus erythematosus-like (SLE-like) syndrome. Aside from the recent report of a cardiac patient who developed the syndrome while on PA and who had a prolonged half-life of metabolism for PA, the evidence is inconclusive. Kosowsky and co-workers reported that 14 of 26 (53%) patients who required PA therapy for 3 months or longer developed untoward side effects. Of these, 12 subjects had arthralgias and/or rash, and ten of the 12 had a positive LE preparation.

Table 3. Half-life of Metabolism, Elimination, and Excretion of PA in 21 Subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>PA Metab t½ (hr)</th>
<th>PA Elim t½ (hr)</th>
<th>PA Excret t½ (hr)</th>
<th>PA dose (mg)</th>
<th>PA* Recov (mg)</th>
<th>NAPA* Recov (mg)</th>
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<td>Mean ± sd</td>
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<td>5.1 ± 1.18</td>
<td>734.3 ± 110.43</td>
<td>442.4 ± 84.37</td>
<td>145.4 ± 75.29</td>
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<td>Mean ± sd</td>
<td>10.9 ± 2.19</td>
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<td>5.5 ± 0.93</td>
<td>736.9 ± 84.56</td>
<td>398.7 ± 54.28</td>
<td>206.5 ± 61.85</td>
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*PA (mg) or NAPA (mg) recovered in 0-24 hour urine collection.

Abbreviations: = Metab = metabolism; Elim = elimination; Excret = excretion; Recov = recovered.
If it can be determined that the SLE-like syndrome occurs only in slow acetylators, PA therapy probably should be avoided entirely in slow acetylators but not from fast acetylators. This is an important distinction. The choice of efficacious antiarrhythmic drugs is very limited and the other agents available for long-term oral antiarrhythmic therapy such as diphenylhydantoin, quinidine, or propranolol also have limitations. To determine if acetylator phenotype can be used to predict PA toxicity, it is critical to have as specific a means as possible to identify individuals with a slow acetylation phenotype. For other drugs such as INH, SMZ, and dapsone, phenotype can be determined from the ratio of metabolite to drug in timed urine or plasma samples, since for each of these other drugs a large fraction is excreted as acetylated metabolite. This technique, however, may be inadequate for PA because of the relatively low fractional excretion of its metabolite, NAPA, after a PA dose even in fast acetylators (fig. 1).

Several of our normal volunteers illustrate classification errors using the method of White and Price-Evans for SMZ. L.B., R.L., A.W., and R.W. each had a half-life of metabolism for SMZ and PA that would not have been predicted from the percent of Ac-SMZ recovered. In addition, the half-life of metabolism for PA for each of these subjects was similar (range 12.8 to 13.9 hours), yet each had marked variation in the percent of Ac-SMZ recovered (range: 55.8 to 80.1%). This evidence indicates that phenotyping by the half-life of metabolism is preferable to basing phenotype on percent of acetylated metabolite in partial or total recovery of urine samples or on any method using the ratio of NAPA/PA in a selected blood or urine sample. Two other of our subjects, A.S. and F.B., illustrated another problem — marked difference between the SMZ acetylation phenotype and the half-life of metabolism of SMZ compared to the same indices of PA. These two subjects probably represent different acetylation rates for the two drugs rather than classification errors. Thus, even the most precise method for classifying phenotype, namely the half-life of metabolism, may be affected by environmental factors such as different drugs, studied on separate days. These subjects underscore the importance of phenotyping by using the specific drug in question rather than a prototype drug, which in this case was SMZ.

Since the 21 subjects in the present study are too few to clearly define whether the PA acetylates has a bimodal distribution, the literature was reviewed. Karlsson has reported on the percent of NAPA recovered in 29 normal volunteers and Gibson on 14 normal volunteers. Each of these investigators measured the percent of NAPA recovered in the 0–24 hour urine samples following an oral dose of PA. A frequency histogram of 64 subjects derived from the data accumulated from the work of Gibson and Karlsson in these two previous studies plus the present study is illustrated in figure 3. This histogram does not demonstrate a bimodal distribution for PA. Further, the correlation between the half-life of metabolism for SMZ and PA (r = 0.47) is weaker than that between the fraction of acetylated SMZ and PA (r = 0.66) (fig. 2). If the metabolism of SMZ and PA is under the control of a bimodally distributed acetylation, then phenotyping by half-life of metabolism, which should be a more precise classification method, should have a stronger r value than by the fraction of acetylated metabolite. The relationship between the t½ of metabolism of PA and SMZ has an r value lower than 0.66, indicating a finding that lends support to the argument that PA is not under the control of a bimodally distributed enzyme. It may be that the 64 individuals studied so far are not representative of the population at large. This hypothesis is supported by studies which compared PA acetylation with other drugs that are acetylated by the bimodally distributed acetylates.

Another explanation for the failure to confirm bimodal distribution is that the method for phenotyping which was used is too error prone. Thus, the question of whether the enzyme accounting for acetylation of PA is the same as that for the drugs INH, SMZ, and dapsone has not been resolved. Studies in more subjects utilizing half-life of metabolism for phenotyping, and studies to determine if most subjects who have developed the SLE-like syndrome are slow acetylators, may answer these important questions in the future.

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The Effects of Minoxidil on Pulmonary and Systemic Hemodynamics in Hypertensive Man

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SUMMARY Pulmonary hypertension has been described as a possible complication of the antihypertensive vasodilator, minoxidil. A prospective study was undertaken in seven severely hypertensive patients refractory to multiple drug therapy. Treatment was initiated with fixed doses of hydrochlorothiazide (100 mg/day) and propranolol (160 mg/day) for a control period. Mean systemic arterial pressure, cardiac output, and pulmonary artery pressure were then compared before and after the addition of acute (5 days) and chronic (2 month) therapy with minoxidil.

DIRECT-ACTING VASODILATORS are frequently used in the treatment of arterial hypertension. Hydralazine has been the only antihypertensive oral vasodilator available and two disadvantages have been associated with its use: inadequate potency in severely hypertensive patients and the development of a lupus erythematosus-like syndrome at doses greater than 200 mg/d. In contrast, the vasodilator minoxidil (6-amino-1, 2-dihydro-1-hydroxy-2-imino piperidino-pyrimidine) has been demonstrated to be more potent and more efficacious than hydralazine1, 2 and has not been associated with the development of positive LE preps and antinuclear antibodies.2, 1, 8

Treatment with vasodilators has been associated with tachycardia due to reflex adrenergic stimulation,1 and with sodium retention,1 and increased plasma renin activity.8 In addition to these side effects common to vasodilators, minoxidil has been implicated in the development of pulmonary hypertension.4, 5 Since vasodilators are useful not only in the treatment of hypertension but also in the management of refractory congestive heart failure, angina, and even cardiogenic shock, it is important to evaluate the hemodynamic effects of such agents on the pulmonary as well as systemic circulation. The present study was designed to compare mean pulmonary artery and capillary wedge pressures, cardiac output, and pulmonary artery resistance before and after acute (5 days) and chronic (2 month) minoxidil administration in severely hypertensive humans.

Mean arterial blood pressure decreased from a control value of 135 mm Hg to a value of 104 mm Hg acutely and 108 mm Hg chronically. Significant increases in mean cardiac output occurred with minoxidil therapy (from 4.2 L/min control to 5.4 L/min acutely and 5.1 L/min chronically) despite concomitant propranolol treatment. Mean pulmonary artery pressure did not increase either acutely or chronically. The data suggest that in patients with normal pulmonary hemodynamics prior to treatment, pulmonary hypertension does not develop during two months of minoxidil therapy.

Methods

Patient Characteristics

Seven patients were studied at the Clinical Research Center of the Indiana University Hospital. The studies were approved by the Indiana University Human Use Committee and informed consent was obtained from each patient. Participation in the present study was not a precondition for treatment with minoxidil. The only criterion for entrance to the study was severe hypertension (as evidenced by outpatient diastolic pressures > 115 mm Hg) not controlled by maximally tolerated doses of several antihypertensive drugs (as indicated in table 1).
The relationship between the metabolism of procainamide and sulfamethazine.
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