Effect of Khat chewing on the bioavailability of ampicillin and amoxycillin

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The study examined the effect of Khat chewing on ampicillin and amoxycillin bioavailability following the administration of a 500 mg single dose of each antibiotic at different times relative to Khat chewing. Using a urinary excretion method the bioavailabilities of ampicillin and amoxycillin were determined in eight healthy adult male Yemeni volunteers. The extent and rate of ampicillin bioavailability were reduced significantly by Khat chewing except when administered 2 h after the Khat chewing session. However, the bioavailability of amoxycillin was only significantly reduced when the antibiotic was taken midway through the Khat chewing session. It was concluded that the two antibiotics, particularly ampicillin, should be taken 2 h after Khat chewing.

Introduction

Khat (Catha edulis) is a shrub that grows in parts of East Africa and Yemen. The leaves and stem tips are chewed to obtain stimulating effects. Since the effect of Khat rapidly diminishes upon wilting, the chewing habit has, until recently, been restricted to countries in which Khat is grown. During the last decades, however, due to the development of highway networks and the availability of air transport, the chewing habit has spread considerably in countries where Khat does not grow. Shipments of Khat have even been observed by custom authorities in France, Denmark, Great Britain and USA. The widespread chewing of Khat in Yemen is a habit that has a deep-rooted sociocultural tradition. The major constituents of Khat leaves include more than six alkaloids, which are the main determinants of the effects of Khat on the CNS, tannins (7–14%) and flavonoids.

Ampicillin and amoxycillin, are used extensively in Yemen. The present study was aimed primarily at investigating any possible interaction(s) between Khat and ampicillin and amoxycillin.

Materials and methods

Materials

Ampicillin capsules (Hiconcil® 250 mg; Bristol Italiana SUD, SPA under authority of Mead-Johnson; batch no. 2221) were purchased from a local market. Amoxicillin capsules (Pentrexyl® 250 mg; Bristol M yers-Squibb, U K; batch no. M10262) were also purchased. The antibiotic reference substances were kindly supplied by the National Quality Control Laboratory of the Ministry of Public Health, Sana’a, Republic of Yemen. Meals, drinks and Khat (C. edulis) were purchased from the local market. The types and quantities taken by all volunteers throughout the trials were kept the same. The Khat used was one of the commonest types in Yemen, known locally as ‘Sauty’.

Bioavailability studies

Eight healthy adult male Yemeni volunteers participated in the trials (average age and body weight (mean ± s.d.) were 26 ± 2.18 years and 60 ± 5.92 kg, respectively). The trials were conducted using a crossover design with a wash-out period of 7 days, throughout all the trials. The volunteers were instructed not to take any drug(s) for 1 week before or during the trials. Ampicillin and amoxycillin were administered after an overnight fast on empty stomachs, in 500 mg single doses with 250 mL of water. Complete emptying of the bladder just before and at each urine collection after drug taking was ensured. The volunteers were advised to drink 200 mL of water after each
urine collection to effect diuresis. Urine collections were made 0, 1, 2, 3, 4, 5, 6, 7, 8, 10 and 12 h after amoxycillin administration and 0, 1, 2, 3, 4, 5, 6, 7, 8 and 12 h after ampicillin administration.

Each antibiotic was taken on five different occasions as follows: A, agent taken alone under fasting conditions (control); B, agent taken just before Khat chewing; C, agent taken just before Khat chewing together with regular food (and drinks); D, agent taken 2 h before Khat chewing; E, agent taken midway through the 4 h Khat chewing session; F, agent taken 2.0 h after the end of the Khat chewing session. The total volume of urine voided at each collection time was recorded and about 50 mL from each sample was stored at 4°C for 24 h awaiting analysis. The amount of antibiotic excreted unchanged in urine was determined chemically.³ Calibration curves for ampicillin and amoxycillin were constructed in urine in a concentration range of 5–40 mg/L for trials conducted on the same day. The mean calibration factors (mean ± s.d.) for ampicillin and amoxycillin were 36.0 ± 1.4 and 38.34 ± 2.0, respectively.

Ampicillin and amoxycillin bioavailability was assessed using the urinary excretion method. The prerequisites for a valid study were fulfilled, i.e. complete emptying of the bladder at each urine collection time, collection of urine until almost all the agent had been excreted and frequent urine collection.⁴ The percentage dose of the antibiotic excreted unchanged in urine over 12 h (PDE%) and the corresponding mean values for the maximum time taken to reach that peak (TTP, h) were used to describe the extent and rate of the antibiotic bioavailability, respectively.⁵ Data were analysed using Student’s t-test.

Results

The mean percentage doses excreted unchanged (PDE %) as ampicillin, the mean maximum peaks of excretion (MPE, mg/h) and the corresponding mean values for the maximum time taken to reach the peak (TTP, h) following oral administration of the antibiotic at different times with respect to Khat chewing are shown in Table I. In comparison with the control, A, the mean PDE%, MPE and TTP were significantly altered in B, C, D and E (P < 0.05) but not in F, where the mean values of the three parameters were similar to those of A (Table I). The mean PDE%, MPE and TTP were comparable for conditions B, C, D and E (Table I). These results indicate that both the extent (PDE%) and the rate (MPE, TTP) of ampicillin bioavailability were substantially reduced by Khat chewing, except when the antibiotic was taken 2 h after chewing Khat (Table I). The reduction of ampicillin bioavailability was most pronounced when the drug was administered midway through the 4 h Khat chewing session (condition E).

The mean PDE% and MPE values were comparable when amoxycillin was administered under conditions A, B, C, D and F (Table II). However, the mean PDE% and MPE values when amoxycillin was taken midway through the 4 h Khat chewing session (condition E) were significantly different from the corresponding values for the control condition, A (Table II; P < 0.02). The results indicate that neither the extent nor the rate of amoxycillin bioavailability was affected by Khat chewing except when the antibiotic was taken midway through the 4 h Khat chewing session; amoxycillin bioavailability was lower and occurred more slowly. Hence, unlike ampicillin, amoxycillin bioavailability was reduced only when the antibiotic was taken during Khat chewing (Tables I and II).

Discussion

The pronounced effect(s) of Khat chewing on ampicillin bioavailability in contrast with its rather limited effect(s) on amoxycillin could be explained in terms of the basic differences between the two antibiotics with respect to their bioavailabilities under normal conditions. Following oral administration of equal doses, amoxycillin is bioavail-

<table>
<thead>
<tr>
<th>Trial condition</th>
<th>PDE ± S.E.M., %</th>
<th>MPE ± S.E.M., mg/h</th>
<th>TTP ± S.E.M., h</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>40.09 ± 0.929</td>
<td>67.70 ± 7.27</td>
<td>1.50 ± 0.00</td>
</tr>
<tr>
<td>B</td>
<td>23.79 ± 3.07</td>
<td>42.82 ± 5.26</td>
<td>2.17 ± 0.471</td>
</tr>
<tr>
<td>C</td>
<td>21.03 ± 2.77</td>
<td>38.14 ± 4.93</td>
<td>2.50 ± 0.00</td>
</tr>
<tr>
<td>D</td>
<td>21.78 ± 2.06</td>
<td>54.20 ± 0.650</td>
<td>2.50 ± 0.00</td>
</tr>
<tr>
<td>E</td>
<td>20.31 ± 0.690</td>
<td>40.65 ± 1.575</td>
<td>2.50 ± 0.433</td>
</tr>
<tr>
<td>F</td>
<td>35.29 ± 3.90</td>
<td>65.12 ± 5.09</td>
<td>1.50 ± 0.00</td>
</tr>
</tbody>
</table>

*See text.

³ Mean percentage dose excreted unchanged.

⁴ Mean maximum peak excretion.

⁵ Mean time to reach peak.
Effect of Khat chewing on drug bioavailability

Table II. The effects of Khat chewing on the bioavailability of amoxycillin

<table>
<thead>
<tr>
<th>Trial condition</th>
<th>PDE ± S.E.M., %</th>
<th>MPE ± S.E.M., mg/h</th>
<th>TTP ± S.E.M., h</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>62.54 ± 3.421</td>
<td>80.31 ± 14.958</td>
<td>1.50 ± 0.183</td>
</tr>
<tr>
<td>B</td>
<td>53.73 ± 4.883</td>
<td>82.62 ± 16.607</td>
<td>1.50 ± 0.327</td>
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<tr>
<td>C</td>
<td>57.06 ± 4.023</td>
<td>78.41 ± 9.521</td>
<td>2.50 ± 0.350</td>
</tr>
<tr>
<td>D</td>
<td>56.91 ± 2.981</td>
<td>73.94 ± 13.329</td>
<td>1.50 ± 0.378</td>
</tr>
<tr>
<td>E</td>
<td>48.83 ± 4.620</td>
<td>66.90 ± 8.275</td>
<td>2.00 ± 0.295</td>
</tr>
<tr>
<td>F</td>
<td>54.12 ± 4.611</td>
<td>75.39 ± 10.204</td>
<td>2.50 ± 0.267</td>
</tr>
</tbody>
</table>

a, b, c, d See footnotes for Table I.

able to a substantially greater extent and at a much higher rate than ampicillin. Up to 70% of the dose of amoxycillin can be absorbed, compared with a maximum of about 40% for ampicillin. Moreover, concurrent administration of ampicillin with food reduces its absorption significantly, whereas amoxycillin absorption is unaffected. The observed pronounced reduction of ampicillin absorption and the limited effect in the case of amoxycillin are consistent with these data.

The mechanisms underlying the effects of Khat chewing probably involve interactions between the antibiotic and the ingredients of Khat leaves, in the gastrointestinal tract. The ingredients of Khat leaves are numerous, but the major and most abundant ingredients include six major alkaloids, tannins (7–14%) and flavonoids. Investigations of the chemical and biological effects of tannins indicate that, of all the components of Khat leaves, these are most likely to be responsible for the observed effects on antibiotic absorption. β-Lactam antibiotics are in general nitrogenous compounds and would be expected to combine with tannins to form insoluble or poorly absorbed complexes. The observed effects of Khat chewing on ampicillin and, to a lesser extent, amoxycillin may be attributable to two effects of these tannins, namely a direct effect, as a result of complexing the antibiotics and converting them to insoluble, non-absorbable compounds, and an indirect effect, as a result of tannins interfering with gut absorption processes.

In conclusion, we recommend that the two antibiotics, particularly ampicillin, are to be taken 2 h after Khat chewing in order to ensure rational utilization of these antibiotics.

References

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