metabolite serum concentrations in order to maintain a steady-state concentration near 100 µg/ml. Based on in vitro experiments the latter was considered adequate for formation of tumouricidal rooperol concentrations. For most patients a daily dose of 2 400 mg (4 capsules 3 times a day) was sufficient.

This study was initiated and sponsored by Essential Sterolin Products according to an agreement entered into with the University of Stellenbosch.

REFERENCES

Accepted 16 May 1995.

A phase I trial of hypoxoside as an oral prodrug for cancer therapy — absence of toxicity


Objective. To assess the toxicity of hypoxoside taken orally by 24 patients with lung cancer.

Design. Open study with patients taking 1 200 - 3 200 mg standardised Hypoxis plant extract (200 mg capsules) per day divided in 3 doses in order to maintain metabolite blood levels near 100 µg/ml.

Participants and setting. Patients with histologically proven squamous, large-cell or adenocarcinoma were hospitalised initially at the radiation oncology ward, Karl Bremer Hospital, Bellville, W. Cape. Thereafter they returned every 2 weeks for full clinical examinations.

Methods. Routine biochemical and haematological measurements were done. Patients underwent regular full clinical examinations including radiographs and computed tomography scanning according to the discretion of the principal investigator.

Results. Nineteen patients on hypoxoside therapy survived for an average of 4 months with progression of their primary tumours and metastases, while 5 survived for more than a year. One of them survived for 5 years and histological examination of the primary lesion showed absence of cancer. No toxic effects, in clinical examinations or biochemical or haematological measurements, were found that could be ascribed to the ingestion of hypoxoside. Only one occasion of possible drug intolerance, with anxiety, nausea, vomiting and diarrhoea, was noted.
**Conclusion.** The absence of toxicity warrants further investigation of hypoxoside as an oral prodrug, especially in patients with slow-growing necrotising tumours that are inoperable and have high concentrations of β-glucuronidase and sulphatase as well as a high sensitivity for rooperol.


Fig. 1 summarises the major results of our research on hypoxoside. It is non-toxic to cancer cells in tissue culture, but when deconjugated to rooperol significant cytotoxicity is found at relatively low concentrations. After oral ingestion no hypoxoside or rooperol are found in the circulation. Only phase II metabolites (glucuronides and sulphates) of rooperol are present. Like the glucoside, the conjugated metabolites are also non-toxic to cells in tissue culture, but they can be activated by treatment with glucuronidase. Since it is known that certain tumours contain relatively high levels of glucuronidase activation of rooperol metabolites at the site of the tumour therefore seemed to be an attractive approach to achieve selectivity in cancer chemotherapy.

**Material and methods**

**Medication and monitoring of serum metabolite levels**

Hypoxoside was supplied by Essential Sterolin Products as a standardised plant extract in capsule form, each capsule containing 200 mg of plant extract. Quality control was assured by high-performance liquid chromatography (HPLC) as described earlier. The hypoxoside content of the standardised plant extract ranged from 50% to 55%. Routine monitoring of metabolite serum levels was done using the HPLC methodology described by Kruger et al.

**Patient eligibility**

Patients above 21 years of age with histologically proven squamous cell, large-cell or adenocarcinoma of the bronchus were included after informed consent according to the Declaration of Helsinki had been obtained. Patients with impaired renal, hepatic or cardiac function or inadequate performance status (H2 or lower) and those who, in the opinion of the investigator, had less than 3 months to live were excluded. The only concomitant anticancer therapy allowed was palliative radiotherapy.

**Study design**

The patients were hospitalised at the radiation oncology ward, Karl Bremer Hospital, Bellville, W. Cape, for the duration of the pharmacokinetic studies. During the long-term therapy stage they returned to hospital every 2 weeks and underwent full clinical examinations including radiographs and computed tomography (CT) scanning according to the discretion of the principal investigator.

**Laboratory analyses**

Biochemical and haematological analyses were performed by the chemical pathology and haematology laboratories at Tygerberg Hospital, Tygerberg, W. Cape.
Results

Patient details
Of the 24 patients who entered the trial 14 were male and 10 female, with ages ranging from 43 to 77 years (mean 56.4 years). Histologically proven diagnoses were adenocarcinoma (9 patients), large-cell carcinoma (9 patients) and squamous cell carcinoma (6 patients). The average survival time for 19 of the patients was 4 months after entering the trial, which agreed with their prognosis without any therapy. Most of them developed metastases.

Table I lists 5 patients who survived longer than expected. Two of them (patients 23 and 24) showed significant arrest of their tumour sizes. Their clinical status will be discussed in more detail (vide infra).

Long-term therapy
Because the serum metabolite concentrations showed considerable interpatient variation owing to apparent zero-order formation of rooperol, the maintenance dose was adjusted when necessary for each patient during hospital visits in order to achieve combined metabolite blood levels near 100 µg/ml. According to in vitro experiments this concentration was considered adequate for activation of the metabolites to tumouricidal rooperol concentrations. The minimum and maximum maintenance doses required were 1 200 and 3 200 mg standardised plant extract per day divided into 3 equal doses every 8 hours. For most patients a daily dose of 2 400 mg plant extract (4 capsules 3 times a day) was sufficient.

Biochemical and haematological data
Figs 2 - 4 provide summaries of all the biochemical and haematological data collected from the patients while they were on long-term therapy. The vertical bars in the figures represent the mean ± 1 standard deviation (SD) of the value measured during intervals of approximately 30 days.

Since 19 of the 24 patients survived less than 1 year it must be realised that the data presented in Figs 2 - 4 are the trends of the mean values in a decreasing population. Table II shows the distribution of surviving patients at monthly intervals and hence the sample sizes at each time.

Table II. Number of patients in the trial at various time intervals (refer to Figs 2 - 4)

<table>
<thead>
<tr>
<th>Time (d)</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>60</td>
<td>16</td>
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</tr>
<tr>
<td>400</td>
<td>4</td>
</tr>
<tr>
<td>600</td>
<td>3</td>
</tr>
</tbody>
</table>

Values of the liver enzymes alanine transaminase (ALT), aspartate transaminase (AST) and lactate dehydrogenase (LD) stayed within normal limits, while mean values of enzymes sensitive to metastases were above normal. Several patients also abused alcohol periodically (Fig. 2).

Table I. Details of patients entered in the trial who survived longer than expected

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Survival time (mo.)</th>
<th>Medical treatment before entering trial</th>
<th>Major clinical events in course of trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>47</td>
<td>F</td>
<td>Large-cell carcinoma</td>
<td>22, 19.5</td>
<td>50 Gy ¹³⁷Co</td>
<td>Partial collapse of lung with small pleural effusion. Clinically well after 5 mo. Developed widespread metastases</td>
</tr>
<tr>
<td>21</td>
<td>54</td>
<td>M</td>
<td>Large-cell carcinoma</td>
<td>15, 13.3</td>
<td>Partial resection</td>
<td>Clinically well except for alcohol abuse as reflected in liver enzyme levels. Elected to leave trial</td>
</tr>
<tr>
<td>22</td>
<td>57</td>
<td>M</td>
<td>Squamous carcinoma</td>
<td>15.5, 12</td>
<td>Inoperable tumour</td>
<td>Gradual progression of tumour. 20 Gy ¹³⁷Co on days 330 - 335 resulted in a marked reduction of tumour size. Developed liver metastases</td>
</tr>
<tr>
<td>23</td>
<td>77</td>
<td>M</td>
<td>Squamous carcinoma</td>
<td>42, 35</td>
<td>50 Gy ¹³⁷Co</td>
<td>Clinically well except for dyspnoea on exertion. Death due to cerebrovascular haemorrhage</td>
</tr>
<tr>
<td>24</td>
<td>49</td>
<td>M</td>
<td>Adeno-carcinoma</td>
<td>63, 60</td>
<td>25 Gy ¹³⁷Co</td>
<td>Large tumour with destruction of 3 - 5 ribs. Clinically well except for sporadic alcohol abuse. CT scan showed reversal of rib destruction after 2 yrs. Died of TB pneumonia. Histological examination of autopsy material showed absence of cancer</td>
</tr>
</tbody>
</table>
Fig. 2. Liver enzyme activity of all the patients in the trial. Each point represents the average of all values obtained on a monthly basis with 1 SD shown as a vertical bar. The shaded areas depict the upper and lower normal limits for the population.

Fig. 3. Serum protein concentrations of all the patients in the trial, plotted as in Fig. 2.

increased marginally and the lymphocyte count decreased slightly. The platelet count stayed remarkably constant.

The absence of any adverse effect of hypoxoside on the values reported above has been verified by specialists in the Departments of Chemical Pathology and Haematology at Tygerberg Hospital.
Clinical status of patients 23 and 24

Since these 2 patients survived the longest while on hypoxoside they underwent a full neurological examination together with the normal regular clinical examinations during the 30th month. No evidence of neurotoxicity resulting from hypoxoside ingestion was found after clinical evaluation by the Neurology Department at Tygerberg Hospital.

Fig. 5 shows chronological CT scans of the tumour in case 24. It is clear that the initial lesions of the ribs reversed to a large extent, together with a reduction in original tumour mass. During this period the alkaline phosphatase levels fell to normal. The patient died of TB pneumonia resulting from tuberculosis after 5 years on hypoxoside therapy (approximately 1 g per day). Histological examination of tissue taken at autopsy showed that all organs (kidney, liver, bone marrow, colon, intestine, brain, spleen) were normal, and surprisingly no cancer could be detected in the fibrotic, cystic lesion in the lung.

Other measurements

Regular measurements of blood pressure and temperature showed no abnormalities. Body mass also stayed constant except when patients developed cachexia in the terminal phase. Serial electrocardiograms also failed to demonstrate any evidence of cardiotoxicity of hypoxoside as confirmed by the Cardiology Department at Tygerberg Hospital.

Side-effects

One patient experienced possible drug intolerance on day 171 of the trial when the serum concentration of hypoxoside metabolites rose to 163 μg/ml. Anxiety, nausea, vomiting, diarrhoea, dyspnoea and rigors were associated with a doubling in the LD and alkaline phosphatase values. The patient stopped taking the drug and the symptoms subsided after 4 - 6 hours. The dose was then reduced from 2 400 mg to 1 200 mg per day and the drug was tolerated without further incidents for another 36 days, after which the patient died of cardiorespiratory failure.
Targeted chemotherapy for parasite infestations in rural black preschool children

M. Taylor, G. Pillai, J. D. Kvalsvig

Objective. To investigate whether targeted chemotherapy can reduce parasite prevalence rates in rural black preschool children.

Design. The study consisted of a before/after trial. Stool and urine samples were analysed on four occasions over a 21-week period.

Setting. Creches in two rural areas of southern KwaZulu/Natal (coastal and inland).

Patients. Two hundred children of 4-6 years of age attending 19 creches in the area.

Intervention. Targeted chemotherapy used albendazole for nematode infestations, praziquantel for trematode and cestode infestations and metronidazole for protozoal infections was administered twice at an interval of 14 weeks.

Main outcome measure. Prevalence rates.

Results. The prevalences of Ascaris lumbricoides, Trichuris trichiura and Necator americanus infestation decreased significantly after treatment. Reinfection rates 12 weeks after treatment were 16% for A. lumbricoides, 33% for T. trichiura, 24% for Giardia lamblia and 3% for N. americanus. No reinfection was noted for Schistosoma haematobium, Hymenolepis or Taenia species.

Conclusion. The study suggests that parasite prevalence rates in children can be reduced by the administration of appropriate chemotherapy at regular intervals. However, the provision of clean water and adequate sewerage facilities remains a high priority for black communities living in rural areas of South Africa.


Although the mortality rate associated with parasite infestations is negligible, morbidity such as impaired physical and mental development is significant. This is confirmed by studies on nematode and cestode infestation in children. In Jamaica prevalence and intensity of infection with Trichuris trichiura were found by Nokes et al. to be greater among academically less able pupils. Bovin et al. reported that after successful treatment for infestation with serious types of chronic intestinal parasites children in Zaire...