The Effects of Oxidised Starch on Blood and Faecal Nitrogen in Uraemia

C GIORDANO, R ESPOSITO, M PLUVIO
Naples University Policlinico, Naples, Italy

INTRODUCTION

Our previous work has reported the physico-chemical characteristics of oxystarch and its reactivity towards ammonia and urea (Giordano et al, 1971). Methods of preparation have been published by us (Giordano et al, 1971). We have also undertaken initial clinical trials and have shown that oxystarch lowers BUN and increases faecal nitrogen excretion (Giordano et al, 1971) in patients with uraemia.

We were prompted to determine the source of the increased faecal nitrogen excretion with oxystarch treatment even though the lowering of BUN suggested that this was urea or ammonia.

To study this point we have followed a suggestion of Dr Friedman (person communication) and used a nitrogen-free diet. This study was completed by following the behaviour of BUN and of blood ammonia in two patients on and off oxystarch. In vitro competitive reactivity for urea or ammonia was also studied.

MATERIALS AND METHODS

Three chronic uraemic patients with a creatinine clearance (Ccr) between 10 and 18 ml/min were subjected to a nitrogen-free diet for a one week period (period A), followed by either starch or oxystarch, one after the other for two further periods each of one week (periods B and C).

The nitrogen-free diet supplied 45 cal/kg body weight (bw) and no proteins or aminoacids whatsoever.

Faecal nitrogen was estimated by the usual Kjeldahl method.

Two other patients with a GFR of 8 and 11 ml/min were treated on and off with oxystarch in order to follow blood ammonia.

In vitro competitive reactivity of urea and ammonia was determined in the following way.

Aliquots of oxystarch (1.2 mM) were placed in test tubes with 5 ml of
buffer at pH 1, the solutions containing respectively 0.5 mM of urea, 0.5 and 0.25 mM of ammonia and 0.25 mM of urea. For each run there was a starch test as blank. The reaction lasted 24h and was at room temperature.

RESULTS

The results of study on the nitrogen-free diet are summarised in Figures 1, 2 and 3. In all these figures it is shown that during oxystarch administration faecal nitrogen excretion increases as compared with the period of starch administration. Since the faecal nitrogen excretion induced by oxystarch in patients given nitrogen-free diet is of the same magnitude as that found in patients given a diet containing protein, we conclude that the nitrogen excess is not to be ascribed to either proteins or aminoacids bound to oxystarch while in the gastrointestinal tract.

In Figure 4 data are found concerning blood ammonia and BUN behaviour in a representative uraemic subject who was followed for 124 days. It is clearly apparent that when oxystarch is being given BUN and blood ammonia decrease, the latter to undetectable amounts, and when starch is being given blood ammonia values resume.

To the bottom of this figure faecal nitrogen excretion data repeat the usual pattern of increase of nitrogen during oxystarch administration.

![Graph showing faecal nitrogen excretion](image)

**Figure 1**

A = N-free diet
B = N-free diet + starch
C = N-free diet + oxystarch
Figure 2

Figure 3

A = N-free diet
B = N-free diet + starch
C = N-free diet + oxystarch
In Table I competitive reactivity of oxystarch towards urea and ammonia are shown.

It is seen that both urea and ammonia if allowed to react separately against oxystarch show the same degree of reactivity.

On the other hand when both urea and ammonia are together and allowed to react with oxystarch there is no evidence of competition. These data are, however, preliminary and have to be extended with isotopic studies.

Table I. Compared Urea and Ammonia Pickup by Oxystarch (OXY)

<table>
<thead>
<tr>
<th>OXY (mM)</th>
<th>Urea (mM)</th>
<th>Ammonia (mM)</th>
<th>% Urea bound</th>
<th>% Ammonia bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2</td>
<td>0.5</td>
<td>0.5</td>
<td>38</td>
<td>36</td>
</tr>
<tr>
<td>1.2</td>
<td>0.25</td>
<td>0.25</td>
<td>22</td>
<td>19</td>
</tr>
</tbody>
</table>

Ammonia and urea solutions 0.2M
Reaction at pH 1 and at room temperature

DISCUSSION
Excess of faecal nitrogen in uraemic subjects given oxystarch may derive from proteins or aminoacids in the diet, or may be due to either urea or ammonia or both from the gastrointestinal tract. However, the alimentary origin of excess of faecal nitrogen can be excluded in view of the data per-
taining to the nitrogen-free diet. In fact, in these conditions, faecal nitrogen excretion on oxystarch completely overlaps that obtained in patients nourished with a regular protein diet.

In vitro data have indicated that oxystarch reacts equally with both urea and ammonia.

These data are confirmed in the study of blood urea nitrogen (BUN) and blood ammonia. Both these levels drop on oxystarch and are resumed on starch.

In conclusion, oxystarch has proved so far to be a gastrointestinal sorbent which traps urea and ammonia in the gastrointestinal tract leading to an increase in faecal nitrogen excretion and a reduced BUN. Since the patients did not experience adverse reactions while on oxystarch its use may be of benefit either to space dialysis or to remove excess waste nitrogen in patients allowed an excessive protein diet.

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OPEN DISCUSSION

K FJELLSSTRÖM (Uppsala): Oxidised starch is a polyaldehyde, is it not? What is the procedure for oxidation of this starch? What type of oxidation are you performing?

GIORDANO: If we need dealdehyde starch we take into account one configuration only — the same configuration in which oxystarch is found in an acidic media. The molecular arrangement of oxystarch in a neutral medium is hemiacetal close form which is why it is not chemically dealdehyde starch. The method of oxidising starch has been published in the book of the Symposium dedicated to Gastro-Sorbents by the NIH: sodium metaperiodate is the oxidising agent. To prevent overoxidation the ratio should be 0.9 of the oxidising agent to one Mol of starch.

FJELLSSTRÖM: Thank you. What I was really trying to say was that if this is an aldehyde compound that you are giving to the patients, then the result of the chemical reaction is obviously a Schiff's base produced by aldehyde and
amino groups; it must follow that the oxystarch that you are giving to the patients binds either the food protein or other proteins.

Would it not be more simple to reduce the amount of protein that you are giving the patients, rather than giving them both protein and starch which will not only bind the ammonia but the amino groups as well?

GIORDANO: In answer to the last question which suggests that oxystarch binds to the amino group of aminoacids and proteins, I should like to state that this possibility is ruled out by means of a simple experiment. This experiment involves giving oxystarch mixed with aminoacids every day for a month to the patient and measuring the amount of aminoacids that are excreted via the faeces, and the remainder left circulating in the blood. The result of this experiment proves that the affinity of oxystarch for the amino group is quite different. To emphasise this point I would add that in the data we have presented here today it has been shown that the problem of the derivation of excess nitrogen in the faeces is not connected with the dietary nitrogen.

R KLUTHE (Chairman): Dr Giordano, you mentioned that there is a possibility of combining oxystarch with charcoal. Did you use this in patients and do you have any results available?

GIORDANO: We have spent a considerable time studying the possibility of combining oxystarch and charcoal for regenerating dialysis fluid. The prime problem with this has been that oxystarch is soluble, and when the two compounds are combined they each retain their individual characteristics. Once we can overcome the solubility of the oxystarch, we feel that this application will be most valid.

A ROODVOETS (Haarlem): Your results suggest that the treatment with oxystarch could also be useful in encephalopathy due to hepatic failure. Do you have any results in patients with this form of treatment? How is the treatment tolerated by the patients?

GIORDANO: With regard to your first question, we have treated one patient who had terminal renal failure on haemodialysis, who also had encephalopathy due to terminal cirrhosis. This patient was given 30g oxystarch per day, and although we did not observe a significant decrease in blood ammonia concentration, we did have a significant increase in total nitrogen excretion in the faeces. The oxystarch was very well tolerated by these patients, and no diarrhoea was present.

A GORDON (Los Angeles): What was the effect of the administration of oxy-
GIORDANO: As there was a decrease in plasma urea nitrogen excretion we waited for a decrease in urinary NPN. In two patients there was a decrease in urinary nitrogen, and a decrease in urinary NPN, as a total expression of excretion.
Increased Nitrogen Removal from the Intestinal Tract of Uraemic Patients

N K MAN, T DRUEKE, J PARIS, C ELIZALDE MONTEVERDE, M RONDON NUCETE, J ZINGRAFF, P JUNGERS

Hôpital Necker, Paris, France

Attempts to remove uraemic waste products via the gastrointestinal tract have been made by numerous workers with varying success (Hamburger et al, 1950; Schloerb, 1959; Drüeke et al, 1972; Ganeval et al, 1973). The binding by oxidised starch (oxystarch) of ammonia derived from intestinal urea synthesis was investigated by Giordano et al (1969) and by Sparks et al (1971). Our purpose was to test the ammonia binding capacity of commercially available oxystarch in a clinical trial and to evaluate its effect on net nitrogen removal. If sufficient quantities could be extracted oxystarch could be of great value in the treatment of patients with advanced renal failure.

METHODS

Twelve patients with advanced chronic uraemia were selected for study. Clinical data on these subjects at the onset of study are summarised in Table I.

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Age (years) (mean and range)</th>
<th>Creatinine clearance (ml/mn) (mean and range)</th>
<th>Plasma urea N (mg/100ml) (mean and range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>45 (17 - 65)</td>
<td>4.1 (1.1 - 6.2)</td>
<td>114 (71 - 165)</td>
</tr>
</tbody>
</table>

Metabolic balance studies were conducted with the patients taking a low protein diet (0.5g protein/kg body weight/day). Nitrogen (N) content was calculated from tables and was verified by analysis of a single day's diet, homogenised in water. No correction for N balance was made for occasional vomiting before breakfast. When vomiting occurred later in the day in any
subject the balance data of that day were omitted. Calculated caloric intake
was in all cases over 1,800 cal daily. No antibiotics were given during the
study. The nature of the study was explained and the consent of each patient
obtained before investigation.

For 6 to 8 days (control period) 8 patients received the diet described
above and then for 6 to 8 days an identical diet supplemented by 30g oxidised
starch (oxystarch) ('Sumstar-190', Miles Lab Inc) orally, in three equally
divided doses. BUN and plasma creatinine were determined every day or
every other day. Urinary output was measured and urine analysis for urea,
creatinine, uric acid and protein was performed daily. Dialysis of faeces
in vivo was performed as described by Wrong et al (1965). Three out of the
8 patients swallowed 4 to 6 dialysing capsules daily over the two periods of
study. The bags contained in the capsules were removed from the stool spe-
cimen either at emission or after thawing out of frozen stools and the fluid
contained in them was then analysed immediately. Stool collections for the
control period began at least one week after starting the low protein diet in
the centre and 2 days after administration of oxystarch for the oxystarch
period. In the patients who were given dialysing bags, stool collections began
2 days after swallowing capsules. Each specimen of stool was weighed, re-
frigerated immediately after emission, and frozen 1 to 10 hours later. Daily
stool weight was calculated by averaging stool weight over each period of
study. Pooled total N analyses of faeces were performed at the end of the
experiments.

As well as the low protein diet described for all the patients in the study
(0.5g/kg body wt/day) 4 patients received 3 to 5g methyl cellulose daily, and
3 patients received 20 to 35g lactulose daily. All these seven patients' stools
were treated by faecal dialysis. Patients in whom no increase in stool weight
was obtained with these doses were excluded from this study.

Nitrogen balance was calculated according to Walser et al (1973) using
the formula

$$b_N = D - P - C$$

where $b_N$ is the body N pool or corrected N balance, D is dietary N, P is
urinary protein N and C is non protein N (NPN) appearance. The urea N
appearance has been defined as the sum of urinary urea N excretion and
change in the urea N pool. Urea space was assumed to be 60% of initial body
weight.

Total N in the faeces was determined using Kjeldahl’s method. Ammonia
(i.e, the sum of $\text{NH}_4^+$ and $\text{NH}_3$), urea, creatinine, uric acid, calcium, phos-
phorus, bicarbonate and protein were determined with the Technicon Auto
Analyzer; pH was measured with the Tacusse pH meter (type TS 4 N).
RESULTS

Urea N appearance and N balance. Under treatment with oxystarch, mean 
urea N appearance (2.73 $\pm$ 0.90 g/day) decreased significantly ($P < 0.02$) when 
compared to the control period (3.89 $\pm$ 0.83 g/day) without oxystarch (Table II).

Table II. Mean daily faecal output, mean daily faecal N excretion and 
mean daily urea N appearance of 8 uraemic patients receiving 
a low protein diet (control) and then an identical diet supplemented by 30 g oxystarch daily for an identical period of time 
(6 to 8 days).

<table>
<thead>
<tr>
<th></th>
<th>Faecal volume (g/day)</th>
<th>Faecal N excretion (g/day)</th>
<th>Urea N appearance (g/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 8)</td>
<td>95 $\pm$ 35</td>
<td>1.08 $\pm$ 0.42</td>
<td>3.89 $\pm$ 0.83</td>
</tr>
<tr>
<td>Oxystarch (n = 8)</td>
<td>233 $\pm$ 89</td>
<td>2.09 $\pm$ 0.63</td>
<td>2.73 $\pm$ 0.90</td>
</tr>
<tr>
<td>P</td>
<td>$&lt; 0.01$</td>
<td>$&lt; 0.01$</td>
<td>$&lt; 0.02$</td>
</tr>
</tbody>
</table>

1 = number of patients

Figure 1. Daily calculated urea N pool, daily faecal N excretion and daily urinary NPN 
before and after oxystarch administration in patient LV. Straight lines were drawn 
visually through the points of urea N pool. The dotted lines indicate means of faecal 
N excretion over the two periods.
Figure 1 shows a representative patient’s data. Increase in faecal volume was accompanied by decrease in urea N of the pool and in urinary NPN when subject LV received a low protein diet plus 30g oxystarch daily. The increase in mean stool total N excretion was associated with a decrease in the mean urea N appearance in all patients. The ratio of the difference of the daily means of control urea N appearance and oxystarch urea N appearance to the difference of oxystarch faecal total N and control faecal total N was calculated as follows:

\[
\frac{3.89 - 2.73 \text{ (g N per day)}}{2.09 - 1.08 \text{ (g N per day)}} = 1.15
\]

Mean net N balance was found to be less negative under oxystarch treatment (- 1.15g/day) when compared to the control period (- 0.67g/day). Figure 2 shows the improvement of corrected N balance of an individual patient, subject MO, when receiving 30g oxystarch daily. This improvement is the result of decreased plasma urea N concentration and urinary NPN excretion and

![Graph showing daily plasma urea N, plasma creatinine N, faecal total N, urinary NPN and corrected N balance in patient MO before and after treatment with oxystarch.](image)
occurs in spite of increased faecal total N excretion. Plasma creatinine N concentration remained unchanged over the two periods.

**N excretion.** A significant increase (P < 0.01) in mean faecal total N excretion (2.09 ± 0.63g/day) was observed during treatment with 30g oxystarch daily when compared to the control period (1.08 ± 0.42g/day) without oxystarch; this increase was accompanied by a significant increase (P < 0.01) in mean stool volume (233 ± 89g/day) when compared to control (95 ± 35g/day) (Table III). A comparable increase in mean total N excretion in the

<table>
<thead>
<tr>
<th></th>
<th>Faecal volume (g/day)</th>
<th>Faecal N excretion (g/day)</th>
<th>Ammonia concentration (mM/l)</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>95 ± 35 (n = 8)</td>
<td>1.08 ± 0.42 (n = 8)</td>
<td>57 ± 20 (n. obs = 24)</td>
<td>6.8 ± 0.6 (n. obs = 11)</td>
</tr>
<tr>
<td>Oxystarch</td>
<td>233 ± 89 (n = 8)</td>
<td>2.09 ± 0.63 (n = 8)</td>
<td>23 ± 17 (n. obs = 26)</td>
<td>6.4 ± 0.5 (n. obs = 11)</td>
</tr>
<tr>
<td>P</td>
<td>&lt; 0.01</td>
<td>&lt; 0.01</td>
<td>&lt; 0.001</td>
<td>NS</td>
</tr>
</tbody>
</table>

n = number of patients; n. obs = number of observations

**Table IV.** Mean (and range) daily faecal volume and daily faecal N excretion of 3 uraemic patients receiving a low protein diet (control) and then an identical diet supplemented by 20 to 35g lactulose daily for an identical period of time (6 to 8 days). Mean stool water ammonia concentration and mean pH values are indicated for each period.

<table>
<thead>
<tr>
<th></th>
<th>Faecal volume (g/day)</th>
<th>Faecal N excretion (g/day)</th>
<th>Ammonia concentration (mM/l)</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>55 (86-111) (n = 3)</td>
<td>1.52 (1.16-1.75) (n = 3)</td>
<td>59 ± 21 (n. obs = 20)</td>
<td>6.9 ± 0.8 (n. obs = 9)</td>
</tr>
<tr>
<td>Lactulose</td>
<td>192 (83-315) (n = 3)</td>
<td>2.90 (1.29-4.02) (n = 3)</td>
<td>26 ± 6 (n. obs = 21)</td>
<td>6.5 ± 0.3 (n. obs = 8)</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
<td>NS</td>
</tr>
</tbody>
</table>

n = number of patients; n. obs = number of observations
faeces 2.90g/day) and in mean stool volume 192g/day) was observed during treatment with 20 to 35g lactulose per day when compared to mean total N excretion (1.52g/day) and to mean stool volume 55g/day) during the control period (Table IV). No such increase in mean total N excretion in the faeces (1.34g/day) could be detected when the diet was supplemented by 3 to 5g of methylcellulose daily, a dose sufficient to increase mean stool volume two-fold to 129g/day. Mean faecal total N excretion was 1.20g/day in the control period without methylcellulose (Table V).

Table V. Mean (and range) daily faecal volume and daily faecal N excretion of 4 uraemic patients receiving a low protein diet (control) and then an identical diet supplemented by 3 to 5g methylcellulose daily for an identical period of time (6 to 8 days). Mean stool water ammonia concentration and mean pH values are indicated for each period.

<table>
<thead>
<tr>
<th></th>
<th>Faecal volume (g/day)</th>
<th>Faecal N excretion (g/day)</th>
<th>Ammonia concentration (mM/l)</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>64 (29-84)</td>
<td>1.20 (0.83-1.75)</td>
<td>43 ± 23 (n. obs = 39)</td>
<td>6.5 ± 1.0 (n. obs = 13)</td>
</tr>
<tr>
<td>Methylcellulose</td>
<td>129 (57-166)</td>
<td>1.34 (0.55-1.85)</td>
<td>35 ± 29 (n. obs = 34)</td>
<td>6.6 ± 0.9 (n. obs = 12)</td>
</tr>
</tbody>
</table>

\( n = \) number of patients; \( n. \ obs = \) number of observations

**pH.** A decrease in mean pH values was observed during oxystarch (6.4 ± 0.5 - Table III) and lactulose (6.5 ± 0.3 - Table IV) treatment but the difference from control values (6.8 ± 0.6; 6.9 ± 0.8 respectively) was not statistically significant. No difference was found between mean pH values of the methylcellulose period (6.5 ± 1.0) and those of the control period (6.6 ± 0.9 - Table V).

**Ammonia.** Mean faecal total ammonia concentration was significantly lower (\( P < 0.001 \)) during treatment with oxystarch (23 ± 17 mM/l - Table III) and with lactulose (26 ± 6 mM/l - Table IV) than in the respective control periods (57 ± 20 mM/l; 59 ± 21 mM/l). A decrease in mean faecal total ammonia concentration was also observed during the methylcellulose period (35 ± 29 mM/l). This decrease, however, was not statistically significant when compared to control values (43 ± 23 mM/l - Table V).
DISCUSSION

The present data confirm the increase in faecal total N excretion in uraemic patients when receiving an oral daily dose of oxystarch, as previously reported by Giordano and Esposito (1972) and by Sparks et al (1971) in animal experiments. In vitro studies of these authors suggested that the observed increase was due at least partly to intestinal binding of ammonia by oxystarch. Increased intestinal binding and elimination of ammonia derived from urea synthesis may contribute to an improvement of the uraemic state.

The increase in intestinal total N excretion during treatment with oxystarch was accompanied by an increase in mean daily stool volume. No such increase in intestinal total N excretion was observed in patients when oxystarch was replaced by methyl cellulose, an aperient that increases mean daily stool volume to an extent comparable to that obtained with oxystarch, when given in doses stated above. Thus, increased stool volume alone is not sufficient to explain increased N elimination. Increased stool volume and increased faecal total N excretion were also observed with lactulose. Lactulose, however, provoked diarrhoea in all 3 patients studied, whereas diarrhoea or intestinal irritation never occurred with oxystarch. Increased N elimination with diarrhoeic stools might be due mainly to incompletely digested protein and to increased epithelial and bacterial protein elimination rather than to increased ammonia elimination. The decreased ammonia concentration in dialysing bags recovered from lactulose treated patients is compatible with this view and with that of others (Agostini et al, 1972). Decreased ammonia concentration in stools from oxystarch treated patients in the absence of diarrhoea and in the absence of decreased transit time may be accounted for by ammonia binding by oxystarch. Decreased ammonia formation from decreased urea degradation seems to be excluded since urea concentration in the dialysing bags was constantly below detectable concentrations (10 mg/100 ml) with the method employed. Increased stool volume alone does not explain decreased faecal ammonia concentration when one is considering the large amount of ammonia formed daily in the intestine.

An effect of varying pH conditions on intestinal ammonia elimination has been reported elsewhere (Castell & Moore, 1971; Agostini et al, 1972; Down et al, 1972). The effect of lactulose on plasma ammonia concentration in the cirrhotic patient has been interpreted as resulting from decreasing the pH and increasing the ammonia concentration of the colonic fluid in this condition (Elkington et al, 1969). The present data, in agreement with Agostini et al (1972) do not confirm this hypothesis. The lack of significant pH decrease with lactulose in the present study could be partially due to the uraemic state. The non-significant decrease in pH of dialysed fluid of the faeces under oxystarch treatment could be due in part to acid breakdown products resulting
from depolymerisation of oxystarch. There is strong evidence, however, against the hypothesis that depolymerisation is important since the calculated mean ammonia N adsorption by oxystarch after intestinal passage in vivo corresponds to that bound in vitro under similar conditions of pH and simulated intestinal milieu (unpublished data).

It is interesting to look for a possible correlation between increase in faecal total N (FTN) elimination and decrease in urea N appearance (UNA). The ratio of the daily means of the difference of control and oxystarch - UNA, to that of the difference of oxystarch and control - FTN, is near to 1.0. This observation may be taken as an indirect proof of the hypothesis that oxystarch binds ammonia derived from urealysis. The magnitude of additional urea thus eliminated by the intestinal route may be calculated as 1.01g urea N or 2.15g urea per day. Thus patients with advanced renal failure treated with oxystarch may be given diets with less severe protein restriction, and this could lead to an improvement in N balance.

CONCLUSIONS

Indirect evidence is given that oxystarch binds intestinal ammonia. Faecal pH change does not play a role in the intestinal elimination of ammonia under oxystarch and lactulose treatment of the uraemic patient.

Oxystarch administration may be helpful in the management of chronic renal failure. Further study with prolonged oxystarch treatment is indicated. More stable preparations of oxystarch and of other ammonia binding poly-aldehyde substances (Sparks et al, 1972) may considerably improve the results.

ACKNOWLEDGMENT

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