Sanguinarine, Hydroxybutyrate Dehydrogenase and Fatigue in Epidemic Dropsy: A Retrospective Study of an Outbreak and its Control from Gujarat, India

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Abstract

Objective: We report an outbreak of epidemic dropsy following ingestion of cooking groundnut-oil adulterated with Argemone oil.

Methods: We describe 40 patients (18 families) from three towns in Gujarat in 1998, affected with epidemic dropsy during an outbreak and its control measures. They were successfully treated with supportive measures and antioxidants. The outbreak control measures used were active and passive surveillance, media campaigns, and action against traders.

Results: Oedema, erythema, cutaneous flush, fatigue, and tachycardia were present. ESR was high. Hydroxybutyrate dehydrogenase levels (165 U/l in 33 patients), reported for the first time, showed significant rise and persisted at 1-month (128 U/l) indicating long-term cardiac toxicity. We detected in serum and urine of 25 patients, sanguinarine (2.5 and 1.4 mg/dl respectively) which at 1-month had returned to trace levels, thus confirming the consumption of oil contaminated with Argemone oil. Fatigue persisted at one month in 80%, and at six months in 38%. Groundnut oil contamination with Argemone mexicana oil was detected.

Conclusion: Groundnut oil (used in cooking) contaminated with Argemone mexicana oil was the cause of epidemic dropsy. The health department controlled the outbreak with surveillance, stopping the mixing of argemone oil, and action against culprits. There were no deaths.

Introduction

Epidemic dropsy due to ingestion of mustard oil adulterated with Argemone oil (AO) has been known since 1877 and reported in 1951 from north Indian states of Bihar and Madhya Pradesh[1]. The seeds of Argemone Mexicana (Mexican poppy/ prickly yellow poppy) resemble mustard seeds [Illustration 1 fig.]. An outbreak of epidemic dropsy detected from small focal areas of Modasa & Dhansura towns of Sabarkantha, and Godhara city of Panchmahal districts from Gujarat, India after a span of 43 years[2] in 1998 was surprising, since in Gujarat groundnut oil is consumed and not mustard oil. We describe clinical features of dropsy along with blood & urine levels of toxic ingredient Sanguinarine, serum hydroxybutyrate dehydrogenase (HBDH) levels for the first time, and epidemic control measures implemented successfully.

Methods

We studied forty cases from 18 families, detected during 6-17 September 1998 and recorded the type, brand and duration of oil consumption. Fasting blood and urine samples from patients and others (non-dropsy patients), and follow-up samples after one month from patients, were collected for estimation of hydroxybutyrate dehydrogenase (HBDH) and other biochemical and hematological investigations. Serum sanguinarine levels were estimated by thin-layer chromatography, initially and after one month in patients. The patients were managed symptomatically with protein rich diet, antioxidants, diuretics, antihistaminic, vitamin supplements and timolol eye drops as indicated. They were followed up at one and six months.

The epidemic was controlled by active (home visits) and passive surveillance (wide publicity, leaflet distribution, awareness creation), identification of source of contamination, destroying of contaminated groundnut oil and strict action in the form of filing of court cases against traders indulging in contamination and their arrests. Three more cases were detected after one month in October from two geographically unconnected districts (Mehsana, Junagadh) and were managed similarly. Since then no case has been reported from Gujarat state.

Results

There were 40 patients- 17 male, 23 female (no one was pregnant), and seven children.

Clinical features: The mean pulse rate was 95 ±12. Blood pressure was normal. Burning sensation in legs was present in eight (20%). All had oedema feet or
As the seeds of mustard and argemone look

In animal studies on rats, Babu has

Mean hemoglobin was 10.5 ±1.49

gerat. Liver, kidney[4],

Sanguinarine was found in serum and

Oedema is a symptom in all studies. Burning

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suggests that there is a mismatch between free

peroxidase activity is observed in dropsy patients. This

glutathione reductase and glutathione-s-transferase

retinyl esters, superoxide desmutase, catalase,

antioxidant capacity, alpha-tocopherol, retinol and

transport of glucose. Decrease in plasma total

hepatic cytochrome p-450, and decreases the active

Cytotoxic sanguinarine inhibits the Na+K+ ATPase &

skin, heart, lung and eyes are the target organs.

Pathology- The toxicity is dose related. Liver, kidney[4],

skin, heart, lung and eyes are the target organs.

Cytotoxic sanguinarine inhibits the Na+K+ ATPase &

hepatic cytochrome p-450, and decreases the active

transport of glucose. Decrease in plasma total

antioxidant capacity, alpha-tocopherol, retinol and

retinyl esters, superoxide desmutase, catalase,

glutathione reductase and glutathione-s-transferase

with a concomitant increase (69%) in glutathione

peroxidase activity is observed in dropsy patients. This

suggests that there is a mismatch between free

radicals formation and enzymatic and non-enzymatic

antioxidant scavengers, which causes oxidative
damage to proteins and lipids in dropsy patients[5-7].

Prostaglandin, and histamine release due to

suppression of histaminase, plays a role in the

pathogenesis of skin manifestations & oedema.

Clinical- Oedema is a symptom in all studies. Burning

sensation in feet and tingling were present but no

neurological lesion could be detected. Due to early

case-detection, none of our patients developed severe

congestive heart failure that is an important prognostic

factor for mortality. Sachdev[8] have reported

hypersecretory open angle glaucoma due to

prostaglandin and histamine release.

Hypoalbuminemia due to effect on liver, and dilatation

of capillaries, and anemia presumably due to

increased circulatory volume or toxic effect of alkaloid

on erythrocytes have been observed[9].

Biochemistry- Sanguinarine was found in serum and

urine; and Tandon[10], Shenolikar[11] observed

similar values. In follow-up samples after 1-month it

was extremely low (serum) or not detectable (urine)
due to stoppage of consumption of contaminated oil.
The initial serum HBDH value (mean 165 U/l) in 33
dropsy patients was high as compared to 35

non-dropsy patients (mean 97, p< 0.1). At 1-month

follow-up in 17 patients, decrease in the levels was not

statistically significant (mean 135 vs 128 U/l). This

reflected the persisting of degenerative changes in

cardiac muscles, even after stopping the consumption

of adulterated oil, due to interaction of sanguinarine

with cardiac glycoside receptor sites. This probably

was the cause of fatigue observed, and its persistence

at six months.

Therapy- Extensive public campaign to inform

population from the day of first case and identification

of source of contamination and control of adulteration

resulted in rapid resolution of epidemic, no deaths and

fewer cases, as compared to 1998 dropsy in Delhi

where there were 3000 victims and 60 deaths. Since

then others have validated as part of therapy,

antioxidants that we had used[12]. Three more cases

were observed from two other parts of Gujarat within

two months. No other cases have been seen since

then in Gujarat.

Conclusion

Patients with epidemic dropsy presented with varied

manifestations involving heart, eyes & skin and,

fatigue. Absence of other diseases, high index of

suspicion, history of consumption of loose oil and

involvement of more than one family member played
an important role in suspecting epidemic dropsy. Estimation of serum and urine sanguinarine led to a definite diagnosis. Serum hydroxybutyrate dehydrogenase was elevated and persisted at follow-up. The patients were treated with supportive measures and anti-oxidant vitamins. The outbreak was controlled in a short time with concerted effort by the state food and health departments.

**Key Messages:**
1. Dropsy leads to cardiac toxicity as shown by increased levels of HBDH, which remain high for weeks. Sanguinarine in blood and urine is eliminated after stopping consumption of contaminated oil. It takes months for complete recovery to occur.
2. It is possible to control the outbreak of dropsy in a short time, with extensive public campaign and by identification of source of contamination, leading to fewer cases and no deaths.
3. Contamination of groundnut oil with argemone oil can also cause dropsy.
4. Antioxidants may be useful to treat epidemic dropsy.
5. Fatigue as a complaint was present in all, and in more than one third, it persisted at six months. Role of sanguinarine in fatigue syndrome should be explored.

**Policy implications:**
1. Sale of loose-unpacked cooking oil should be monitored for contamination with argemone oil. Cooking oil should be used in moderation. Facility to test edible oil by competent authority should be available in each region.
2. Strict enforcement of the Indian Food Adulteration Act and exemplary punishment to unscrupulous traders is the measure to prevent future occurrences.[12]
3. Zero tolerance policy for sanguinarine presence in food for man as well as animals.[3]

**References**


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Illustrations

Illustration 1

Seeds of mustard and Mexican poppy

Illustration 1
Illustration 2

Sanguinarine and HBDH values

(a) Serum HBDH values: mean ± sd (number) as U/l at 37°C

<table>
<thead>
<tr>
<th></th>
<th>Initial</th>
<th>1-month</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dropsy patients</td>
<td>134.88 ±31.37 (17)</td>
<td>127.94 ±19.2 (17)</td>
<td>0.326</td>
</tr>
<tr>
<td>Other patients</td>
<td>164.8 ±78.3 (33)*</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>96.5 ±19.2 (35)*</td>
<td>-</td>
<td>*p &lt;0.01</td>
</tr>
</tbody>
</table>

(b) Sanguinarine values: range, #median (number), *mean ± sd (n)

<table>
<thead>
<tr>
<th></th>
<th>Present study</th>
<th>Tandon10</th>
<th>Shenolikar11</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>1-month</td>
<td>Initial</td>
</tr>
<tr>
<td>Serum µg/dl</td>
<td>0.45- 5.5, #1.98 (10)</td>
<td>ND- 0.19, #0.05 (10)</td>
<td></td>
</tr>
<tr>
<td>Urine µg/l</td>
<td>0.1- 5.9, #0.96 (12)</td>
<td>ND- ND (12)</td>
<td></td>
</tr>
<tr>
<td>Serum µg/dl</td>
<td>2.53 ±1.48 (25)*</td>
<td>-</td>
<td>1.2- 3.6 (3)</td>
</tr>
<tr>
<td>Urine µg/l</td>
<td>1.42 ±1.27 (25)*</td>
<td>-</td>
<td>0.4- 3.6 (8)</td>
</tr>
</tbody>
</table>

HBDH- hydroxybutyrate dehydrogenase, ND- not detected
Illustration 3

Cardiac manifestations compared

Table 3: Cardiac manifestations (%) in epidemic dropsy

<table>
<thead>
<tr>
<th>Manifestations</th>
<th>Present study</th>
<th>Shah\textsuperscript{13}</th>
<th>Wadia\textsuperscript{14}</th>
<th>Misra\textsuperscript{15}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachycardia</td>
<td>75</td>
<td>100</td>
<td>13.56</td>
<td>94.28</td>
</tr>
<tr>
<td>Chest pain</td>
<td>2.5</td>
<td>8.95</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>15</td>
<td>4.67</td>
<td>12.56</td>
<td>65.71</td>
</tr>
<tr>
<td>CHF/Gallop/3\textsuperscript{rd} HS</td>
<td>2.5</td>
<td>4.67</td>
<td>5.76</td>
<td>65.71</td>
</tr>
<tr>
<td>Systolic murmur</td>
<td>12.5</td>
<td>4.47</td>
<td>13.56</td>
<td>22.85</td>
</tr>
</tbody>
</table>

CHF- congestive heart failure; HS- heart sound.

Illustration 4

Other clinical features

Table 2: Clinical features (40 patients) in epidemic dropsy

<table>
<thead>
<tr>
<th>Manifestations</th>
<th>Number (%)</th>
<th>Duration (days)</th>
<th>range (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>mean ± sd</td>
<td></td>
</tr>
<tr>
<td>Oedema feet/legs</td>
<td>37 (92.5)</td>
<td>9.89 ± 9.51</td>
<td>3-30</td>
</tr>
<tr>
<td>Erythema</td>
<td>22 (55.0)</td>
<td>7.65 ± 7.36</td>
<td>2-30</td>
</tr>
<tr>
<td>Cutaneous flush</td>
<td>17 (42.5)</td>
<td>9.88 ± 9.77</td>
<td>2-30</td>
</tr>
<tr>
<td>Pain in legs</td>
<td>14 (35.0)</td>
<td>10.0 ± 9.91</td>
<td>2-30</td>
</tr>
<tr>
<td>Tenderness</td>
<td>7 (17.5)</td>
<td>11.43 ± 6.11</td>
<td>2-15</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>6 (15.0)</td>
<td>7.83 ± 3.11</td>
<td>3-14</td>
</tr>
<tr>
<td>Tingling</td>
<td>6 (15.0)</td>
<td>7.0 ± 6.54</td>
<td>1-15</td>
</tr>
<tr>
<td>Pigmentation</td>
<td>6 (15.0)</td>
<td>7.17 ± 4.62</td>
<td>3-15</td>
</tr>
<tr>
<td>Warmth</td>
<td>5 (5.0)</td>
<td>10.0 ± 6.85</td>
<td>2-15</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (7.5)</td>
<td>3.67 ± 2.89</td>
<td>1-4</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2 (5.0)</td>
<td>6.2 ± 3.49</td>
<td>6-18</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (2.5)</td>
<td>2.0</td>
<td>-</td>
</tr>
</tbody>
</table>
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