Cockayne Syndrome (CS) is a rare, autosomal recessive disorder characterized by small stature, intellectual disability, and features representing accelerated pathologic aging.1 The mean age at death is 8.4 years (B.T.W., unpublished data); rarely, patients survive >30 years. Through the Cockayne Syndrome Natural History Study, we have identified 8 cases of acute hepatic failure after metronidazole administration (representing 8% of our cohort), 3 of which were fatal. Detailed information was available for 4 patients. Metronidazole-induced hepatotoxicity is extremely rare. Our series more than doubles the number of cases reported. We have not identified any patients with CS who have received metronidazole without adverse effects.

Patient 1 was a 19-month-old boy with CS who underwent elective Nissen fundoplication with gastrostomy for gastroesophageal reflux. After discharge, he developed diarrhea. Stool culture was negative, and although an antigen test was positive, the Clostridium difficile toxin assay was negative, that is, there was no evidence of infection. He received empirical intravenous metronidazole, 10 mg/kg every 6 hours for 2.5 days, then 7.5 mg/kg every 6 hours for an additional 3.5 days. No other systemic medication was given. His diarrheal symptoms resolved, and he was discharged. He presented the next day generally unwell, with jaundice and steatorrhea. Liver function tests were markedly deranged (Table 1). Coagulation was also grossly abnormal. Serology for hepatitis B surface antigen, hepatitis C, enterovirus, and adenovirus were negative. Urine, blood, endotracheal, and ascitic cultures were negative. Methicillin-resistant Staphylococcus aureus screen was normal. He developed shock and was intubated, but intensive therapy proved futile. He died 11 days after initial metronidazole administration. Postmortem examination identified extensive hepatic necrosis to be the cause of death. There was no suggestion of liver sepsis. Variable loss of hepatocytes was seen throughout the liver, with
extensive fibrosis in severely affected areas and lobular fibrosis between remaining hepatocytes.

Patients 2 and 3 were twin women, aged 18 years, who had insulin-dependent diabetes as part of their CS. They were treated with empirical oral metronidazole every 8 hours in the community for loose stools, pending results of investigations for gastrointestinal infection. These were negative. After 2 days, blood glucose measurements became elevated and difficult to control, leading to admission on day 4 of metronidazole therapy. On admission, both patients were given a loading dose of 15 mg/kg intravenous metronidazole, followed by 7.5 mg/kg every 8 hours. Liver enzymes were elevated on admission (Table 1) but were thought to be secondary to ischemic damage in the context of metabolic acidosis and shock. Both patients deteriorated rapidly. Again, intensive therapy proved futile. The sisters died within 4 hours of each other, 6 days after initial administration of metronidazole.

Patient 4 is a 21-year-old woman who developed jaundice 2 weeks after becoming generally unwell after 3 days of 400 mg twice-daily oral metronidazole for gastrointestinal bacterial overgrowth (ie, loose stools with no objective evidence of infection). Hepatic function was deranged, with bilirubin and alanine aminotransferase improving, although γ-glutamyl transferase and activated partial thromboplastin time peaked 2 weeks after admission (Fig 1A). During admission, she had a neurometabolic stroke, with hemiparesis and acute on chronic swallowing difficulties, resulting in likely aspiration pneumonia. MRI could not be performed; head computed tomography scan showed no acute changes. This patient survived.

An additional 4 patients received empirical metronidazole for presumed gastrointestinal infection and became systemically unwell, with liver signs. One patient also became acutely nonambulant; this condition gradually resolved over the next year. Liver function gradually recovered after early cessation of metronidazole therapy.

Given this unprecedented adverse drug reaction to metronidazole among patients with CS, we evaluated the effect of this medication on patient and control fibroblasts. Using trypan blue, we found a significant decrease in the proportion of viable cells in the presence of 5 mg/mL metronidazole (Fig 1B). Values represent mean ± SEM for 3 repeats. *Significantly different from controls at day 4 (P < .005 using a 2-tailed Student’s t-test). ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; GGT, γ-glutamyl transferase.

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**TABLE 1**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Total (direct) Bilirubin (mg/dL)</th>
<th>Aspartate Aminotransferase (U/L)</th>
<th>γ-Glutamyl Transferase (U/L)</th>
<th>Alkaline phosphatase (U/L)</th>
<th>Activated Partial Thromboplastin Time (s)</th>
<th>International Normalized Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.0 (1.5–3.0)</td>
<td>3004 (1–10)</td>
<td>3551 (5–105)</td>
<td>6206 (5–310)</td>
<td>2004 (5–104)</td>
<td>0.8 (0.4–1.2)</td>
</tr>
<tr>
<td>2</td>
<td>7.5 (6.7–2.0)</td>
<td>37 (2–15)</td>
<td>35 (2–15)</td>
<td>188 (0–40)</td>
<td>188 (0–40)</td>
<td>0.8 (0.4–1.2)</td>
</tr>
<tr>
<td>3</td>
<td>3.7 (2.4–1.5)</td>
<td>35 (2–15)</td>
<td>35 (2–15)</td>
<td>188 (0–40)</td>
<td>188 (0–40)</td>
<td>0.8 (0.4–1.2)</td>
</tr>
<tr>
<td>4</td>
<td>12.1 (1–10)</td>
<td>344 (1–104)</td>
<td>344 (1–104)</td>
<td>944 (1–104)</td>
<td>944 (1–104)</td>
<td>0.8 (0.4–1.2)</td>
</tr>
</tbody>
</table>

Laboratory reference ranges appear in brackets, [ ] not done.

**FIGURE 1**

A. Close monitoring of liver function tests in patient 4 after admission (ie, 2 weeks after oral metronidazole). Normal ranges appear in Table 1. B. Viability of fibroblasts grown in the presence of 5 mg/mL metronidazole: normal controls (NHDFs and 1BR.3, open symbols) and patients with CS (ENG027 and ENG028, closed symbols). Topical metronidazole preparations are typically 7.5 mg/mL. Values represent mean ± SEM for 3 repeats. *Significantly different from controls at day 4 (P < .005 using a 2-tailed Student’s t-test). ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; GGT, γ-glutamyl transferase.
CS versus control cells after 4 days of treatment with 5 mg/mL metronidazole (Fig 1B), consistent with the time frame of deterioration in our patients.

Loose stools, with or without coexisting constipation, are common in CS (B.T.W., unpublished data), affecting ~30% of patients and occurring independently of gastrointestinal infection. Given the lack of comprehensive information on the natural history and management of CS, it is not surprising that in some cases new-onset diarrhea has been managed preemptively, to prevent clinical deterioration while laboratory investigations seeking objective evidence of infection are carried out. For most patient groups, this course of action would be considered the most prudent, with minimal risk to the patient. Metronidazole is a synthetic nitroimidazole, widely used to treat anaerobic gut infections. It has an excellent safety profile. A handful of cases of metronidazole-induced hepatotoxicity have been reported previously, usually associated with ethanol intake. Hepatotoxicity has been reported for the related drug ornidazole, in the absence of ethanol, suggesting that in some patients an alternative mechanism may be responsible. Neurotoxicity is more widely recognized after metronidazole administration, and onset may be delayed by several weeks. This neurotoxicity produces acute changes on T2-weighted MRI of the brain, particularly in cerebellum and basal ganglia. Interestingly, patients with CS commonly experience hepatic and cerebellar decline (B.T.W., unpublished data). This is the first disorder-specific adverse drug reaction reported in this class of drugs and therefore probably is a consequence of the underlying pathology of CS. Our experimental data indicate that this is a generalized rather than tissue-specific phenomenon. Additional investigation may lead to an improved understanding of the biology of this class of drugs.

CONCLUSIONS

Metronidazole is contraindicated in CS, and intravenous administration may be fatal. Drugs in the same class should be avoided or used only with extreme caution and close monitoring of liver function and coagulation. This monitoring should continue 2 to 4 weeks after last administration.

ACKNOWLEDGMENTS

We thank all affected families for supporting publication. Ethical approval for the Cockayne Syndrome Natural History study was granted by the NRES Committee North East, Newcastle and North Tyneside 2. Written consent was obtained from all families for participation and publication of clinical information.

ABBREVIATION

CS: Cockayne syndrome

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The online version of this article, along with updated information and services, is located on the World Wide Web at: /content/early/2015/08/18/peds.2015-0531