Acetominophen (Tylenol, Paracetamol)

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49.1 Uses

Tylenol is a mild nonnarcotic analgesic and antipyretic agent that is widely used for pain relief and fever reduction. The maximum safe daily dosage is less than 4 g in a 24-h period.

49.2 Mechanism

The precise mechanism of analgesic action has not been clearly defined. Nevertheless, Tylenol appears to produce analgesia by elevation of the pain threshold. The potential mechanism may involve the inhibition of the nitric oxide pathway. In relation to its antipyretic action, acetaminophen has been shown to inhibit endogenous pyrogens and block the formation of central nervous system prostaglandins. Tylenol is also a COX-2 inhibitor, which exerts its therapeutic effects by decreasing the production of thromboxanes. However, centrilobular necrosis can result from abundance of the reactive metabolite of acetaminophen, N-acetyl-*p*-benzoquinone imine, which is formed by cytochrome P-450 by a direct two-electron oxidation of acetaminophen. Ammonia is produced in the gastrointestinal tract from digestion of protein and bacterial metabolism. Normally, ammonia is metabolized primarily in the liver as urea via the urea cycle. However, when the metabolic capacity of the liver is overwhelmed, elimination becomes dependent on the kidneys, brain, and skeletal muscle. Astrocytes metabolize ammonia and glutamate to glutamine via the glutamine synthetase pathways, which leads to an increase in cellular osmolarity and astrocyte swelling. Inflammatory cascades, apoptosis, and various metabolic pathways ensue, resulting in elevation in lactate, loss of cerebral autoregulation, and cerebral edema.

49.3 Discussion

The acute symptoms can be nonspecific, ranging from mild altered mental status to varying degrees of unresponsiveness, with coma and death occurring in severe cases. The toxic levels of glutamine caused by Tylenol overdose predominantly lead to cerebral cortical injury. CT can demonstrate diffuse cerebral edema, which manifests as loss of gray-white mater differentiation, hypoattenuation, and sulcal effacement (Fig. 49.1). MRI, particularly FLAIR, and DWI sequences are useful for depicting acute hyperammonemic encephalopathy. The most common findings on MRI are bilateral symmetric high FLAIR and DWI signal in the cerebral cortex, especially the insular and cingulate cortices, with relative sparring of the perirolandic and occipital regions. In addition, the basal ganglia,

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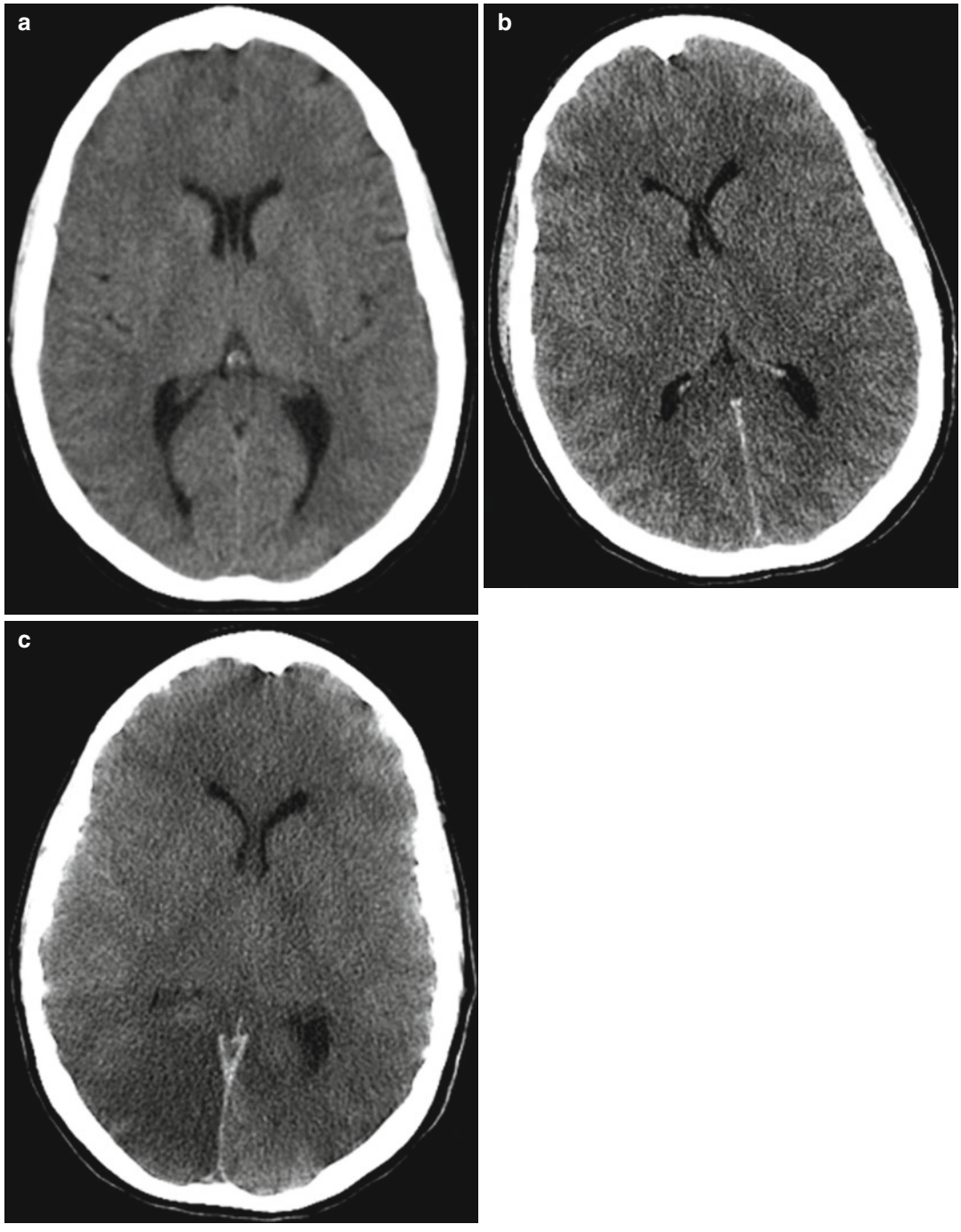

Fig. 49.1 Cerebral edema secondary to fulminant acute liver failure associated with acetaminophen overdose. Axial CT image obtained at the time of presentation soon after ingestion (**a**) demonstrates an unremarkable appearance of the brain. Axial CT images obtained 4 days (**b**) and 7 days (**c**) after ingestion demonstrate progressive loss of gray-white differentiation and severe diffuse cerebral cytotoxic edema secondary to acute liver failure with markedly elevated ammonia levels. There is also progressive effacement of the lateral ventricles secondary to diffuse brain edema

thalamus, and brainstem may also be affected. The high DWI signal can correspond to restricted diffusion. Treatment consists of administration of acetylcysteine, ideally within 8 h of Tylenol ingestion. Thus, prompt diagnosis is crucial. The signal abnormalities in hyperammonemic encephalopathy are potentially reversible with prompt and aggressive treatment, but may also evolve to variable degrees of atrophy in the cingulate and insular cortex after treatment.

49.4 Differential Diagnosis

Other causes of hyperammonemia include acute hepatic encephalopathy from other cases, such as alcohol and valproate toxicity (refer to Chaps. 2 and 28), as well as citrullinemia and proximal urea cycle disorders. Otherwise, the differential considerations for cerebral edema secondary to acetaminophen overdose on imaging include diffuse hypoxic-ischemic injury (Fig. 49.2), posterior reversible encephalopathy syndrome (refer to Chap. 23), seizure activity (Fig. 49.3), and Creutzfeldt-Jakob disease (Fig. 49.4). Seizure activity can result in reversible cortical FLAIR and DWI hyperintensity, which can be localized or generalized, and with or without associated contrast enhancement. Although Creutzfeldt-Jakob disease can produce T2 cortical and/or deep gray matter hyperintensity and restricted diffusion, it classically presents with rapidly progressive dementia.

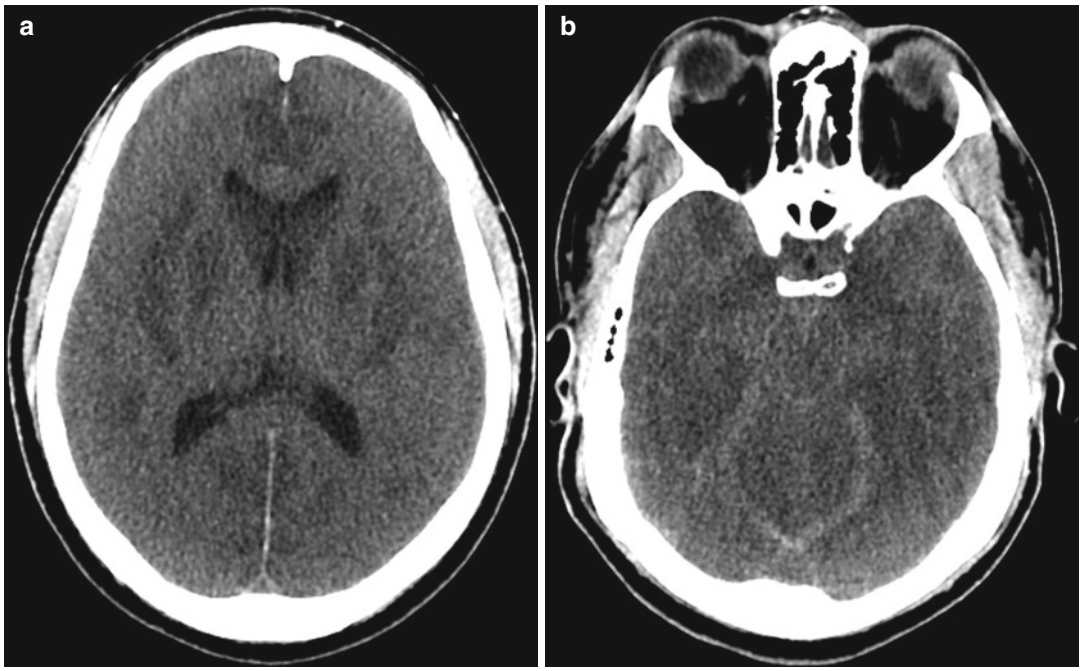

Fig. 49.2 Hypoxic-ischemic encephalopathy. The patient has a history of insulin-dependent diabetes mellitus status post cardiac arrest secondary to DKA status post resuscitation. Axial CT images (**a**, **b**) show diffuse cerebral edema with sulcal, ventricular, and basal cistern effacement, as well as more pronounced areas of hypoattenuation within the bilateral basal ganglia

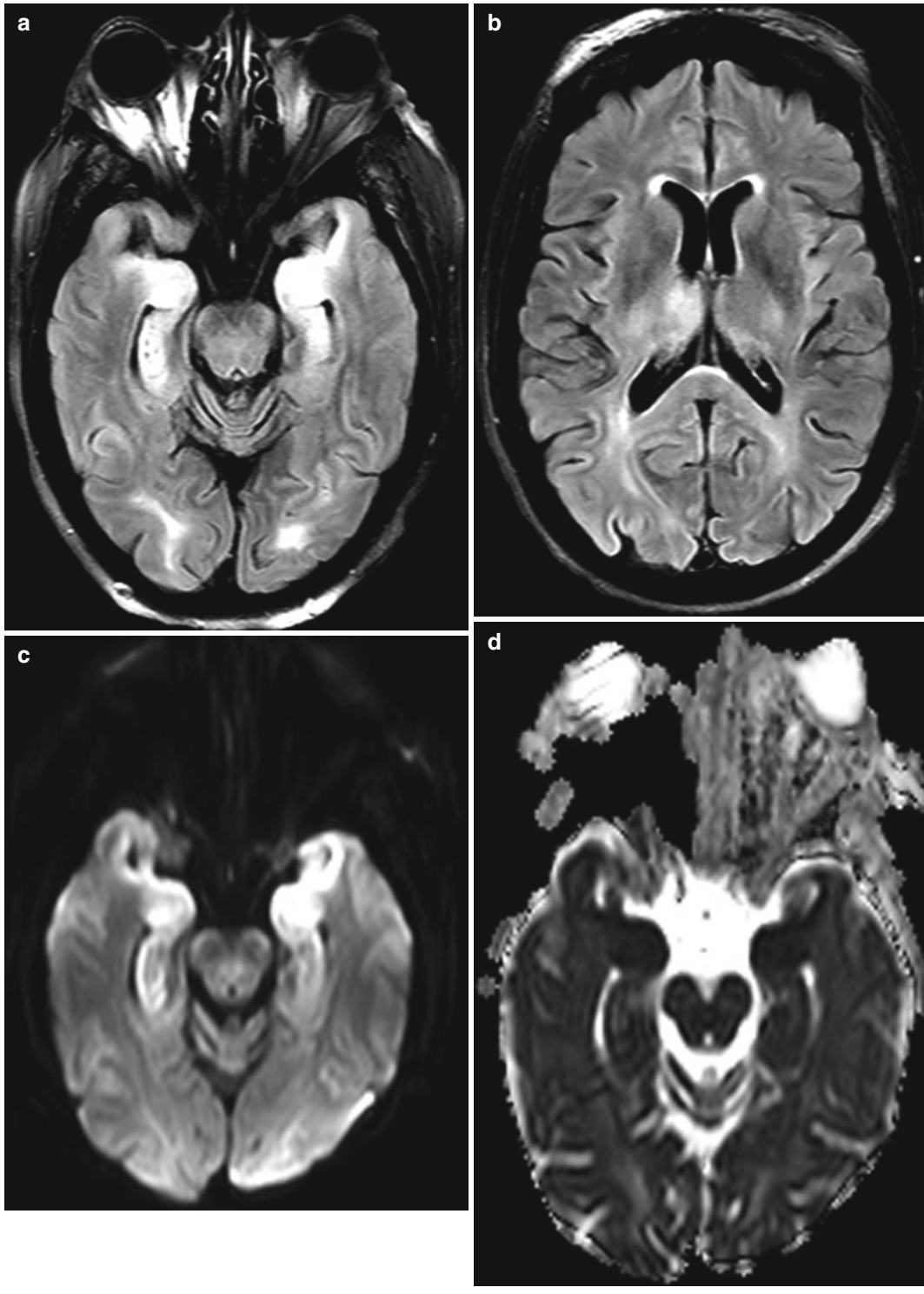

Fig. 49.3 Status epilepticus. Axial FLAIR images (**a**, **b**) show hyperintensity within the bilateral medial temporal lobes and thalami. The DWI (**c**) and ADC map (**d**) show corresponding restricted diffusion

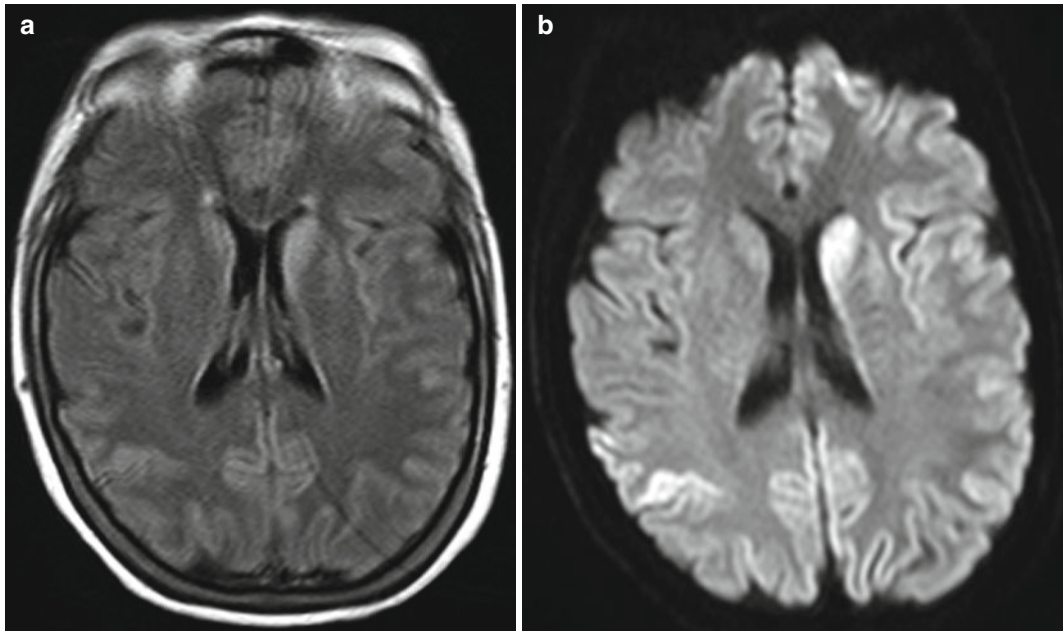

Fig. 49.4 Creutzfeldt-Jakob disease. Axial FLAIR (**a**) and DWI (**b**) sequences show diffuse peripheral and central gray matter hyperintensity involving the cerebral cortex and left caudate head

Suggested Reading

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