

## What is hyoscine N-butylbromide?

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At 9 am on the 23<sup>rd</sup> of November 1910, Dr Harvey Hawley Crippen, an American who had originally trained as a homeopathic doctor, was dispatched to the next world by public hanging in London's Pentonville prison for murdering his minor-celebrity singer wife, Belle. In court, he was described as "quiet, mild and polite, a docile husband and an apparently entirely unremarkable person." His wife appeared to be "a blowsy, heavy-drinking nightmare, vain, bullying and promiscuous." Nonetheless, after she had been missing for some time and suspicions were raised, parts of the unfortunate Mrs Crippen's dissected body were found hidden under their coal cellar, along with traces of poison. Dr Crippen was arrested when he tried to escape to Canada by passenger liner with his mistress, Ethel Le Neve, who had disguised herself (unsuccessfully) as a young boy.<sup>1</sup> The British public was entranced with this story, one which was peppered with glamour, intrigue, murder, adultery, conflict, a high-speed transatlantic chase and pharmacology: Dr Crippen's poison of choice was hyoscine.

In its raw alkaloid state, hyoscine (like atropine) is found in many plants of the genus *Scopolia*, including mandrake (reputedly used by witches in Europe to confer special powers), deadly nightshade, henbane (possibly used by ancient Egyptians for diarrhoea), jimsonweed, Australian corkwood and the various angel's trumpets of South America. All parts of these plants are considered potentially toxic, particularly if ingested unadulterated and/or in larger than homeopathic quantities. Hyoscine extracted from these plants may be crystallised to a hydrobromide, a compound widely used in the late 19<sup>th</sup> and early 20<sup>th</sup> centuries as a sleeping draught.<sup>2</sup> Presumably, Dr Crippen had easy access to this formulation.

Across the Atlantic, at about the same time, Arthur Cushny, a Professor of Pharmacology at the University of Michigan, conducted important experiments *in-vivo*, in healthy volunteers and in psychiatric patients comparing the effects of the two optical isomers of hyoscine hydrobromide in sleeping draughts.<sup>3</sup> He found that the L-isomer was superior to the D-isomer in promoting sleep, concluding that the former had a higher affinity for specific brain receptors. These receptors were subsequently found to be the ubiquitous acetylcholine muscarinic receptors which are essential for eliciting parasympathetic or "rest-digest" responses.<sup>4</sup> Non-selective muscarinic antagonists including hyoscine lead to diverse dose-related autonomic effects such as diminished salivary, bronchial and sweat secretion at low doses,



Dr Crippen and Ethel Le Neve on trial at the Old Bailey, London 1910

tachycardia, pupillary dilation with subsequent increased intra-ocular pressure at higher doses, and inhibition of micturition and decreased gut tone and motility at high doses.<sup>5</sup> It is hyoscine's latter effect as a gastro-intestinal smooth muscle relaxant<sup>6</sup> that has been put to therapeutic use for the symptomatic treatment of functional cramping abdominal pain.<sup>7</sup>

Hyoscine N-butylbromide (HBB) is a highly polar quaternary ammonium derivative of hyoscine - it contains a nitrogen molecule with four different bonds to varying chemical groups - which ultimately implies that unlike Dr Crippen's tertiary amine parent molecule, it is unable to cross the blood brain barrier to exert central nervous system effects.<sup>8,9</sup> It also retains its polar nature regardless of surrounding pH, and is therefore poorly absorbed (8%) after oral intake with a systemic bioavailability of a mere 1%.<sup>10</sup> In theory, this means that the vast majority of HBB or its metabolites are confined to the intended sites of action in the gastrointestinal tract: HBB is mainly distributed on muscle cells of the abdominal and pelvic area as well as in the intramural ganglia of the abdominal organs. Although orally administered HBB is excreted in both the faeces and in the urine, the metabolites excreted via the renal route bind poorly to the muscarinic receptors and are therefore not considered active here.<sup>9</sup>

Oral hyoscine N-butylbromide was first licensed for conditions associated with gastrointestinal spasm in Germany in 1951 under the trade name Buscopan®.<sup>11,12</sup> Although the registration of this drug was based on scanty data, more recent safety and efficacy data from randomised clinical trials have demonstrated

that HBB is effective at relieving abdominal cramps, and may be associated with relatively minor and self-limiting anticholinergic side effects at the recommended dosages.<sup>7,8,10-13</sup> It should be noted that geriatric patients may be especially susceptible to the anticholinergic side effects of constipation, dry mouth and urinary retention.<sup>12</sup>

Successful widespread use as well as accumulation of scientific evidence of oral HBB has paved the way for pharmaceutical reformulation, indication expansion, generic availability as well as rescheduling from prescription only to over-the-counter status in many countries.<sup>8,14,15</sup> In some, oral HBB is currently indicated for the relief of smooth muscle spasm of both the gastrointestinal and genitourinary systems,<sup>11,12,13,16</sup> while the parenteral ampoules for injection are indicated for the relief of acute genitourinary or gastrointestinal spasm (e.g., renal or biliary colic)<sup>11,12,17,18</sup>, or to produce smooth muscle relaxation prior to radiological procedures such as pyelography or other diagnostic procedures where spasm may be a problem (e.g., gastro-duodenal endoscopy).<sup>5,12,19</sup> In South Africa, HBB is licensed for conditions associated with gastro-intestinal spasm only, and is available in oral and injectable formulations.<sup>12,15</sup>

From a pharmacological perspective it is gratifying that hyoscine, under the wings of N-butylbromide, has emerged from its deadly shadow to become a useful therapy for functional cramping abdominal pain, a condition estimated to affect 30% of the Western adult population.<sup>8</sup>

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