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Hyoscine N-Butylbromide (Buscopan®) in the Treatment of Acute Ureteral Colic: What Is the Evidence?

What Is Already Known about This Topic?

- There is a number of publications that investigate the pharmacological effect of hyoscine N-butylbromide (HBB) in the urinary tract in various conditions, either as monotherapy or part of a combined approach, with controversial results.
- An evidence-based approach is required to clarify the role of HBB in the management of acute urinary obstruction.

What Does This Article Add?

- To our knowledge, this is the only study in the literature that looks at all available evidence and provides a succinct statement on the role of HBB in the management of acute ureteral colic.

Key Words

Hyoscine N-butylbromide · Ureteral colic · Spasmolytic · Anticholinergic · Analgesia

Abstract

Objective: To investigate the evidence for the use of hyoscine N-butylbromide (HBB) in the treatment of acute renal colic. **Methods:** A literature search was performed using the keywords 'hyoscine N-butylbromide', 'ureteral colic', 'spasmolytic', 'anticholinergic' and 'analgesia'. The articles were given the appropriate level of evidence according to the Oxford Centre for Evidence-Based Medicine Levels of Evidence guidelines. **Results:** The analgesic effect of HBB as monotherapy is inferior to that of opioids and/or non-steroidal an-

ti-inflammatory drugs (NSAIDs). It does provide an analgesic and antispasmodic effect, but not as long-lasting as NSAIDs. HBB does not serve as an adjunct to opioids. Furthermore, it does not facilitate passage of ureteral stones and has no effect on expulsion rate. **Conclusions:** HBB is often used where urinary tract smooth muscle spasm is thought to be part of the pathophysiological process. According to the evidence, administration of HBB follows non-peer-reviewed protocols which are based on empiric recommendations. Its role is still unclear, as it appears to have no advantage when used as monotherapy over established forms of analgesia. There appears to be a time-dependent relation to pain reduction following parenteral administration, but this needs to be confirmed by more prospective randomized cohorts.

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Introduction

The management of pain from acute urinary obstruction continues to be an expanding field of research and innovation. Pharmacological intervention is the mainstay of initial management. Various categories of medication have been studied during clinical trials, alone or in combination, in order to identify the most efficient first-line treatment of pain due to obstruction by a calculus. HBB is used regularly in some countries to treat a variety of urological conditions, by virtue of its spasmolytic effect on the smooth musculature of the urinary tract [1]. Also described as scopolamine butylbromide or butylscopolamine, it is available both as a prescription drug and as an over-the-counter medicine worldwide. It is extensively used in many fields of medicine, especially in gastroenterology, anesthesia and chronic pain management; yet, the evidence for its specific use and suitability in urology is limited.

This article reviews the available evidence in the literature with regards to its use and role in the management of pain resulting from an acutely obstructing ureteral stone. We performed a literature search by using the keywords 'hyoscine N-butylbromide', 'ureteral colic', 'spasmolytic', 'anticholinergic' and 'analgesia'. The selected articles were given the appropriate level of evidence (LE) according to the Oxford Centre for Evidence-Based Medicine Levels of Evidence guidelines [2] (table 1). Segregation was based on relativity to the effectiveness of HBB in acute renal colic management.

HBB for the Passage of Ureteral Stones

The role of HBB in facilitating ureteral stone passage by acting as a muscle relaxant has been investigated and the results do not support the theory. In a study by Gurbuz et al. [3], 140 patients with stones in the distal ureter were treated with HBB compared to three different alpha 1-adrenergic blockers (doxazosin, terazosin and alfuzosin). The stone expulsion rate was higher in the groups of patients treated with different doses of alpha 1-adrenergic blockers than in the groups that received HBB (LE: 1b). In vitro, HBB is not effective in relaxing isolated human ureteric smooth muscle [1, 4, 5]. Equally, HBB did not affect the elevated ureteral pressure as calibrated by an inflated balloon catheter in anesthetized dogs [6]. The drug had virtually no lasting effect on the ureter nor did it help the passing of stones by reducing friction in vivo in a rabbit model (LE: 2b) [7, 8]. Others support that HBB decreases human ureteric activity somewhat, based on reducing the intravesical pressure following administration

Table 1. Level type of evidence [31]

1a	evidence obtained from meta-analysis of randomized trials
1b	evidence obtained from at least one randomized trial
2a	evidence obtained from one well-designed controlled study without randomization
2b	evidence obtained from at least one other type of well-designed quasi-experimental study
3	evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports
4	evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

[9, 10]. This was further tested in a urodynamic study assessing the effects of a 60 mg dose of intravenously delivered HBB in 10 patients with neurogenic bladder [11] in which the data showed a significant mean increase in bladder capacity and reduced spasm amplitude. This decrease in intravesical pressure was believed to have a secondary effect on pain and spasticity of the urinary system as a whole (LE: 2b). However, the results from three double-blind clinical trials showed no pain relief with HBB monotherapy after laparoscopic sterilization or during/after extracorporeal shock wave lithotripsy (LE: 1b) [12–14]. Patient-controlled analgesic consumption during shock wave lithotripsy was comparable between HBB and placebo [14].

HBB as an Analgesic

Antimuscarinics are often used in the management of ureteral colic, most commonly in combination with conventional analgesia or as part of the analgesic ladder. HBB has been studied in trigger point injection combined with sulpirine and compared to lidocaine. The local anesthetic proved to be significantly more effective (LE: 1a) [15]. It was also investigated as either monotherapy or in combination with desmopressin and was found to be effective in patients with renal colic, with a more pronounced effect when combined (LE: 3) [16]. The addition of HBB to opioids in the management of renal colic was not found to be effective. In a placebo-controlled study of 178 patients by Tomiak et al. [17] (HBB vs. placebo vs. morphine) no reduction of the need for opioids was confirmed (LE: 1b). In a randomized controlled trial with 192 patients, HBB did not reduce the dose or the need for ongoing opioid analgesia in acute renal colic (LE: 1b)

Table 2. Summary of evidence on the use of HBB on acute ureteral colic

	LE
<i>Analgesic effect</i>	
The analgesic effect of HBB as monotherapy is inferior to opioids and/or NSAIDs	1b
HBB does provide an analgesic and antispasmodic effect, but not as long-lasting as NSAIDs	1b
HBB does not serve as an adjunct to opioids	1b
<i>Ureteric stones</i>	
HBB does not facilitate passage of ureteric stones and has no effect on expulsion rate	1b

[18], a finding further supported in a subsequent systematic review (LE: 1a) [19]. Overall, there is insufficient evidence that HBB reduces opioid requirements in this condition (LE: 1b) [20].

Data from prospective and double-blind randomized studies are suggestive of some effect of HBB in prolonging analgesia when combined with non-steroidal anti-inflammatory drugs (NSAIDs). In the prospective study by Khalifa and Sharkawi [21], the combination of HBB with pethidine was superior to diclofenac sodium monotherapy (LE: 1b). Similarly, double-blind studies of HBB with dipyrone (buscopan compositum) versus tenoxicam [22] and flurbiprofen [23] suggest that the synergistic action is effective in providing significant pain relief, although it is suggested that the NSAIDs act more quickly with a longer duration (LE: 1b). In a double-blind clinical trial, 96 patients with renal colic were randomized to either dipyrone sodium (1–2.5 mg), HBB (20 mg) or both (LE: 1b) [24]. HBB was ineffective in reducing pain intensity within 30 min of administration, as assessed by using a visual analog scale (VAS). Thereafter, HBB as a monotherapy was proven responsible for a 33% reduction in VAS score, in contrast to 96% with 2.5 mg dipyrone sodium as a monotherapy. This time-dependent relation to pain reduction following parenteral administration was demonstrated further. HBB was found to be equally effective as 100 mg i.v. tramadol both 30 and 50 min after delivery, and was inferior only to dipyrone ($p < 0.05$) (LE: 1b) [25, 26]. When patients' perception of pain was evaluated, the responses showed a notable difference. About two-thirds of patients (73%) treated with HBB experienced long-lasting pain reduction (of at least 10 mm on the VAS) and as many as 90% rated their treatment as good to very good. It is unclear, however, whether this long-lasting effect was influ-

enced by the natural, gradual decrease of intensity of renal colic with time.

Table 2 provides a summary of the quality of the evidence according to the literature.

Discussion

Renal colic is generated by hyperperistalsis of the obstructed ureter. Peristalsis is modulated by alpha-receptors (contraction), beta-receptors (relaxation) and prostaglandins (PG F2alpha: contraction; PG E1/E2: relaxation). Increases in collecting system pressure and ureteral wall tension are also proposed mechanisms of renal colic [27]. Primate models reveal that distention-mediated activation of renal pelvis mechanoreceptors results in spinothalamic (pain pathway) C fiber excitation. The mean threshold pressure to elicit this primate response was 32 mm Hg. This is similar to the 30 mm Hg proposed threshold for evoking pain in humans [28]. This effect is augmented by the resulting inflammation and edema caused by stone impaction and by increasing ureteral peristalsis as a direct consequence of the obstructing calculus. All these changes constitute the pharmacological targets of the various medications used in the treatment of acute renal colic. In many countries, HBB is often prescribed for treatment of renal colic, usually as adjuvant therapy to NSAIDs and/or opioids [29]. Even if HBB does not appear to have the same effect as NSAIDs [19], it has less cardiac and nephrologic side effects. This could become even more important as diclofenac (and other NSAIDs too) is getting more and more controversially discussed in cardiac-impaired patients since it affects platelet aggregation, which in turn might increase blood loss [30, 31]. For renal insufficiency and cardiac patients it is an alternative to opioids, as long as it is given intravenously and in a systematic fashion. It is also used in protocols to treat bladder spasm, to aid stone expulsion through ureteric relaxation and perioperatively to facilitate ureteroscopy and other endourological procedures such as stent insertion [29, 32]. HBB is a quaternary ammonium compound with anticholinergic properties. It exhibits high affinity for muscarinic receptors and also binds to nicotinic receptors. Inhibition of cholinergic transmission in the abdominal and pelvic parasympathetic ganglia produces the spasmolytic effect in the smooth muscle of gastrointestinal, biliary, urinary tract and female genital organs [33]. It is usually administered parenterally, as oral bioavailability is low, with plasma concentrations measured below the limit of

quantitation. A muscle-relaxing effect has been documented for the renal pelvis in human pharmacological studies after parenteral administration [1, 32]. In contrast, a similar effect could not be demonstrated for the ureter [17].

Conclusion

HBB is often used in the management of urological conditions where urinary tract smooth muscle spasm is thought to be part of the pathophysiological process. According to the evidence, administration of HBB fol-

lows non-peer-reviewed protocols which are based on empiric recommendations. Its role is still unclear, as it appears to have no advantage when used as monotherapy over established forms of analgesia. There is no evidence to date that support its use in combination with opioids in the treatment of acute renal colic. When compared with NSAIDs, the onset of and duration of analgesia with NSAIDs is superior to that of HBB alone. There appears to be a time-dependent relation to pain reduction following parenteral administration, but this needs to be confirmed by more prospective randomized cohorts.

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