

From the Asthma Poliklinik, Free University of West Berlin,
Germany.

INTERMITTENT THERAPY WITH POTASSIUM IODIDE IN CHRONIC OBSTRUCTIVE DISEASE OF THE AIRWAYS

A Review of 10 Years' Experience

By

CHRISTINE BERNECKER

Potassium iodide (KI) is one of the oldest asthma remedies known. *Strümpell* (1844) in his textbook of medicine which has seen many editions and was a standard textbook in Germany for about 30 years mentions KI (1.5-3.0 g and more) as the first remedy for bronchial asthma. Later the substance appears to have lost its popularity, but the B.P.C. still includes KI in low dosage in Ammoniated Potassium Iodide Mixture (150-300 mg per dose) Stramonium and Potassium Iodide Mixture (200 mg per dose). *Alstead* (1939) has compared Pot. iod. (up to 1.8 g) and other expectorants but found all of them useless. More recently *Falliers* (1960) has described a good effect of 900 mg KI in asthmatic children.

Blind or double-blind studies with higher dosages do not seem to have been published. They would be difficult because of the characteristic salty-bitter taste of KI and the persistent metallic taste of iodide secreted in the saliva. It seems unlikely that a placebo with similar taste and after-taste could be found. It seemed worth reviewing the effects and side effects of KI in 2404 patients treated with this substance during the past 10 years.

PATIENTS AND PROCEDURE

The 2404 patients in this series (1184 men, 1120 women and 100 children) were all seen in the Asthma Clinic, in which the total number of patients in ten years was about 6000. These patients were sent by medical practitioners because they were difficult to treat and possibly required corticosteroids. Others were transferred to the clinic after they had been treated as inpatients. A minority came through recommendations of friends. Thus, these 2404 patients had, on the whole, a more severe degree of disease than would be expected elsewhere. They all had chronic obstructive disease of the airways, that is bronchial asthma with hypersecretion or chronic bronchitis. In some of them chronic bronchitis was caused by heart failure and chronic congestion of the pulmonary circulation. Hypersecretion was regarded as present if the patient had cough and/or viscid phlegm or reported that he believed phlegm to be present but could not bring halation or ephedrine, and some were on corticosteroid maintenance. The in it up. Many patients used also other asthma remedies, such as isoprenaline indication for the use of KI was the presence of productive or unproductive morning or evening cough lasting longer than 2 or 3 min., or the feeling of wanting to cough up phlegm without being able to do so.

The routine procedure was as follows: The patient was given an 8 per cent KI solution with instruction to take one tablespoon three times daily (3.6 g/day), preferably in milk or fruit juice (later the instruction was two tablespoons twice daily, 4.8 g) for 4 consecutive days, followed by a 3 day interval. This "interval method" was intended to prevent tolerance. (*Herxheimer 1952*). It proved most convenient for the assessment of the KI effect. In the ideal case the patient's story when he returned after 2 weeks' treatment was that the morning cough was now of much shorter duration, say 5 min. instead of 60 min. and that the phlegm was now loose. This improvement occurred at 12-24 hr after beginning of the treatment and lasted until the end of the fifth day, (the first day of the interval). On the second and third day of the interval the cough usually started to increase again without achieving the intensity it had before the treatment. The difference between the KI period and the interval was often so striking that the patients would spontaneously report it and add that they looked forward to the resuming of KI and the relief it promised. Others merely stressed that the viscosity of the phlegm had clearly increased at the end of the interval. As none of the patients could have anticipated such a course of improvement and subsequent deterioration, this was regarded as strong evidence of the KI effect.

Although many patients responded in this way, there were also other reactions. Some patients deteriorated so much on the second day after stopping the drug that the cough and phlegm were the same as before the treatment. In these cases the period of taking KI was shortened from 4 to 3 days and the interval from 3 to 2 days.

In other patients the cough completely disappeared and did not recur during the interval. In these cases it was assumed that a temporary retention of mucus

had been removed by the KI, and that there was no chronic hypersecretion. The drug was then stopped and the patient instructed to resume it if the cough re-occurred again. There remained a hard core of patients who reported no improvement. In these the dosage of KI was increased every 2 weeks until the desired effect occurred. In many of these the KI solution was stepped up to 16 per cent, 20 per cent, 25 per cent and 30 per cent. (9.6 g, 12 g, 15 g and 18 g/day). In few patients still greater amounts (40 per cent-50 per cent, 24-30 g/day) and in one patient 60 per cent (36 g/day) were successful.

Although in most patients the hypersecretion was greatly improved by KI, there were some in whom the severity of the asthma did not permit the slow process of increasing the dosage of KI. In these cases corticosteroid treatment was started as soon as it was evident that the initial amounts of KI were not sufficient. In some of these patients the hypersecretion ceased after some weeks on the corticosteroid and the KI could then be stopped. In the most severe cases however, KI had to be continued besides the corticosteroid maintenance dose and seemed to keep this at a lower level than would otherwise have been the case.

RESULTS

The 2404 patients included adults between 14 and 86 yr and 100 children between 3 and 14 yrs. The adults are considered in 3 groups:

Group A: 283 patients who were under observation for up to three weeks and then either returned to their family doctor, or failed to keep their next appointment.

Group B: 1207 patients were under observation for longer than 3 weeks and up to 6 months. These were patients in whom either side effects appeared or the treatment was continued by their own doctor.

Group C: The remaining 814 patients required continuous observation over several years often because of cortico-steroid maintenance.

The results in group A were variable, as one would expect with this short period of observation which did not permit the determination of the correct dosage. They varied from improvements in 61 per cent (asthma or chronic bronchitis) to 64 per cent (congestive bronchitis).

The results of group B are given in Table 1.

The results of group C were almost uniformly good, as otherwise the treatment would not have been continued for

TABLE 1

Daily KI amount (g)	Diagnosis	Number of cases	Percentage of		
			no effect	moderate ¹ effect	good ² effect
5-7	asthma or chron. bronchitis	642	5	9	86
	cardiac failure with congestive bronchitis	20	10	30	60
	asthma (children)*	78	3	7	90
9-15	asthma or chron. bronchitis	497	4	16	80
	cardiac failure with congestive bronchitis	23	0	22	78
	asthma (children)	22	0	9	91
18-36	asthma or chron. bronchitis (includ- ing 2 patients with congest. bron.	25	0	13	87

¹ Moderate effect: duration and intensity of cough decreased; cough increased during the KI free interval.

² Good effect: cough almost disappeared; patient is no longer disturbed by it.

* Some children had amounts of 0.3-3 g KI daily.

such long periods. The dosage was sometimes increased if intercurrent respiratory infections occurred which also required antibiotics. After 2 or 3 weeks it usually was possible to return to the previous KI dose.

SIDE EFFECTS

Some side effects appeared immediately after treatment had started and others appeared only after weeks or months.

Immediate Side Effects

1) Swelling of parotid and submandibular salivary glands, often on both sides, with pains sometimes radiating into jaw

and teeth, in some cases combined with swelling of the upper half face, involving one or both eyes, looking like Quincke's oedema (*Harden* 1968). This oedema was seldom hot, sometimes caused one eye to close and disappeared within 2 or 3 days. Possibly the lacrimal glands were involved. (125 patients = 5 per cent).

2) Watery running of the nose (62 patients = 2 per cent).

3) Headache (57 patients = 2 per cent).

These side effects disappeared in about three quarters of the patients after 2 or 3 days without omitting KI. In other cases it was necessary to reduce the dose of KI drastically for a few days and to increase it again gradually until tolerance against these side effects occurred, as it usually did, within 2 weeks. Only in 6 patients such side effects occurred repeatedly.

Side Effects Appearing Later

1) Gastrointestinal upset—loss of appetite, heartburn, nausea, vomiting, midline or right-sided epigastric pain. This complaint occurred seldom during the first month of treatment and mostly after the patients had the same dose for 2 months and longer, up to 6 months. It was dose-dependent, as the following figures show:

TABLE 2

Daily KI dose (g)	Gastrointestinal complaints in all patients of the same dose group (group A, B and C)	
	number of cases	percentage
5-7	133	10.9
9-15	185	17.2
18-36	42	40.7

This complaint regularly disappeared in few days after KI was omitted. In a few cases antacids were given and the symptoms diminished so much that KI could be continued. In

3.4 per cent (of the total of 2404 patients) KI was eventually stopped because of stomach complaints.

Diarrhoea occurred independently of the other gastrointestinal symptoms. It could be stopped by a temporary reduction of the KI dosage.

2) Thyroid disorders: Myxoedema, with or without enlargement of the thyroid, occurred in 12 patients aged 42–78 yr. When clinical grounds made this diagnosis likely, it was confirmed by laboratory tests—serum cholesterol and ecg. Its occurrence seemed dose—dependent, as the following figures show:

TABLE 3

Daily KI dose	Myxoedema in all patients of the same dose group (group A, B and C)	
	number of cases	percentage
5–7	3	0.2
9–15	6	0.6
18–36	3	2.9

In those cases in whom KI, in spite of the myxoedema, could not be withdrawn, the signs of myxoedema were satisfactorily controlled by thyroid preparations. In the others, the signs and symptoms subsided 2–3 weeks after KI had been taken off.

A slight swelling of the thyroid without myxoedema was seen in 4 patients, in whom some minor increase of thyroid size had been noted before KI treatment. Despite continuing KI administration the swelling did not increase further and it cannot be with certainty attributed to the iodide. The same holds good for 3 cases of mild hyperthyroidism which possibly had been present before treatment and which were not influenced by KI. Another group of disorders consisted of iodine acne and styes, urticaria and eczema; there were also a few cases of erythema nodosum. These disorders sometimes required dermatological treatment and/or reduction of the KI dosage.

DISCUSSION

The observations reported here indicate that KI is valuable in cases of bronchial hypersecretion with retention of sputum. In the various groups of patients it improved the cough in between 60-91 per cent of the cases and also decreased the breathlessness.

As blind or double-blind experiments were not possible, it would have appeared desirable to use other objective methods confirming the results, such as measuring the amount of sputum or its viscosity. The first offers little prospect of success, as the amount of sputum in a typical case at first increases and then sharply decreases. This course varies greatly, presumably because it depends on the amount of sputum retained. Also, some of the liquefied sputum is not expectorated but absorbed. This occurs particularly often in children and sometimes in young adults, in whom the cough just disappears although no phlegm is expectorated.

Studies of sputum viscosity have so far been unproductive, mainly because the sputum is not homogeneous and because viscosimetry has still considerable sources of error (*Baldry & Josse 1968, Stresemann 1968*). Little is known about the mechanism of the KI effect. *Stresemann & Schumacher (1963)* have found that iodide appears in the bronchial secretion of man in direct proportion to the iodide plasma concentration. The secretolytic effect of iodide is therefore not caused by the physico-chemical action of the iodide in the sputum. The authors suggest that iodide stimulates the bronchial mucous glands to secrete a more liquid sputum. According to *Lieberman & Kurnick (1964)* iodide accelerates enzymatic proteolysis in vitro, but for this purpose the concentration must be higher than would be provided by the doses used by earlier observers. This seems to justify the high KI doses used by *Herxheimer (1952, 1965)* and in the present series.

Of the many side effects only three are of practical importance. The swelling of the salivary glands can resemble

acute parotitis and is most impressive to the patient. It is possibly brought about through an irritation caused by the strong concentration of iodide in these glands (*Honour et al.* 1952). It is unknown by what mechanism subsequent tolerance to iodide develops. This development occurs so regularly that the disturbance can be taken lightly even if the first appearance of the swelling should cause some initial anxiety.

The stomach complaint is the most frequent one, and it has enforced the withdrawal of the drug in a high percentage of cases, particularly with high dosages (see Table 2). Its reasons are not clear. Some patients seem to develop an intense dislike of the continuous metallic taste in their mouth ("I can stand the taste no longer, my stomach is all upset"). It seems possible that the potassium in KI may cause the complaint, as is known, for instance, from enteric-coated KCl tablets (*Baker et al.* 1964, *Räf* 1965).

Myxoedema has been observed in the past by many authors after KI and iodine containing mixtures, for instance iodopyrin (contained in "Felsol"). There are, however, wide differences of opinion about the frequency of this occurrence. *Begg & Hall* (1963) found, for instance, myxoedema in 6 of 18 (33 per cent) patients who had taken Felsol regularly for 1-22 yrs. *Frey* (1964) found myxoedema in 5 of 6 patients, who had taken ca. 500 g KI/yr for about 10 years. In the present series the percentage is much lower. Even in the 103 patients who had high doses of KI (more than 100 g per week), it does not reach 3 per cent. The reasons for this great difference may be that in the present series, KI has never been given continuously, and this intermittent treatment may act differently from continuous treatment. *Baker & Alcock* (1965) for instance, have found that a certain compound causing cataract in rats did this only if a certain amount of the drug was given every day of the week, but rarely if the same total drug amount was given only on 5 days of the week. Also, the experience of those authors who found a high percentage of myxoedema is limited to very few patients in comparison to the large numbers in the present series. Other reasons may be

the fact that another component of Felsol (phenazone) may have an antithyroid effect.

SUMMARY

1. The results of Potassium Iodide (KI) treatment in 2404 patients with chronic obstructive disease of the airways are reviewed.

2. In a high percentage of the patients the treatment loosened the mucus, considerably shortened the duration of the cough or abolished it and improved the dyspnoea.

3. The reversal of this improvement during the temporary withdrawal of the treatment (interval) is regarded as evidence of the KI effect.

4. The immediate side effects are swelling of the salivary glands, iodine coryza and iodine acne. With appropriate measures they do not prevent continuing KI therapy.

5. The long-term side effects are mainly stomach upsets and myxoedema. They are dose-dependent. The percentage of stomach complaints increases from 10.9 per cent (of 1225 patients) with small doses to 40.7 per cent (of 103 patients) with the highest dosage, in myxoedema from 0.2 per cent (of 1225 patients) to 2.9 per cent (of 103 patients). The danger of myxoedema therefore appears less than suggested by other observers. It can be recognized easily and treated successfully. In 3.4 per cent of the total 2404 patients the KI therapy was abandoned because of stomach complaints.

ACKNOWLEDGEMENTS

This work is the abridged version of a thesis written in German (Bernecker 1969), and my thanks are due to Professor H. Herzheimer and to Dr. A. Herzheimer for helping me with the English version.

REFERENCES

- Alstead, S.*: Lancet 2, 932, 1939.
Baker, D. R., Schrader, W. H. & Hitchcock, C. R.: J.A.M.A. 190, 586, 1964.

- Baker, S. B. de C. & Alcock, S. J.: Proc. Europ. Soc. Study of Drug Toxicity, 6, 213, 1965.
- Baldry, P. E. & Josse, S. E.: Am. Rev. Resp. Dis. 98, 392, 1968.
- Begg, T. B. & Hall, R.: Quart. J. Med., 32, 351, 1963.
- Bernecker, C.: Der Einfluss von Jodkalium bei Bronchialer Hypersecretion: Wirkung und Nebenwirkungen. M.D. Thesis. Freie Universität Berlin, 1969.
- Falliers, C. J., Mc. Cann, W. P., Chai, H., Ellis, E. F. & Yazedi, N. J.: Allergy 38, 183, 1966.
- Frey, H.: Acta endocrin. 47, 105, 1964.
- Harden, R. McG.: Brit. med. J. 1, 160, 1968.
- Herxheimer, H.: Management of Asthma bronchiale, London, (Butterworth), 1952.
- Herxheimer, H.: Fortschr. Med. 83, 853, 1965.
- Honour, A. J., Myant, N. B. & Rowlands, E. N.: Clin. Sci. 11, 447, 1952.
- Lieberman, J. & Kurnick, N. B.: J. Clin. Invest. 43, 1892, 1964.
- Räf, L.: Lancet 2, 593, 1965.
- Stresemann, E. & Schumacher, W.: Klin. Wschr. 41, 751, 1963.
- Stresemann, E.: Klin. Wschr. 46, 1062, 1968.
- Strümpell, A.: Lehrbuch der speziellen Pathologie und Therapie der inneren Krankheiten 19. ed., Leipzig 1914.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.