POISONING BY 2-METHYLBUTYRALDEHYDE (ISOVALERALDEHYDE)

By JOHN F. WILKINSON, M.D., M.Sc., Ph.D., F.R.C.P., F.I.C.

From the Department of Clinical Investigation and Research, Royal Infirmary and University of Manchester

Introduction

In 1937 I had the opportunity of observing the effects on several research workers of accidental exposure to the influence of the vapour of 2-methylbutyraldehyde (isovaleraldehyde).

Circumstances of exposure

2-Methylbutyraldehyde (isovaleraldehyde), $\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!CH{-}CH_2{-}CHO$, is a colourless, pungent-smelling liquid having a boiling point of 92–93° C., and showing the typical chemical behaviour and properties of an aliphatic aldehyde.

In this particular case, it was being prepared by the catalytic dehydrogenation of isoamyl alcohol by a modification of the methods of Bouvealt, and of Sabatier and Senderens.

The method consisted essentially in passing the vapour of isoamyl alcohol up towers containing reduced copper heated to 250–300° C. whereby the following reaction took place:

$$\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!CH{-}CH_2{-}CH_2{-}OH \rightarrow \begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!CH{-}CH_2{-}CHO + H_2.$$

The isovaleraldehyde and some isoamyl alcohol passed into a fractionating column where the alcohol (b.p. 131° C.) was condensed and automatically siphoned back into the still containing the alcohol while isovaleraldehyde passed on and was collected in the receiver.

The whole apparatus was self-contained, but as hydrogen was evolved in the process there was a current of gas with some vapour passing out at the exit tube of the receiver and in subsequent experiments this was exhausted into a fume chamber. This apparatus was usually run for 10–12 hr. on three successive days during which time 5 kg. of crude isovaleraldehyde were produced. This was redistilled yielding two fractions: (*a*) a constant boiling mixture of isovaleraldehyde and water distilling at 75–78° C., which was dried over anhydrous sodium sulphate, and (*b*) almost pure isovaleraldehyde boiling 88–95° C.

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These two fractions were then combined and redistilled with 10% acetic anhydride yielding a distillate of pure 2-methylbutyraldehyde (isovaleraldehyde), b.p. 92–93° C.

These manipulations were carried out mainly in the fume cupboard, but the dehydrogenating apparatus owing to its size was in such a position near a door at one end of the laboratory (which was about 60 ft. long × 30 ft. wide × 25 ft. high) so that the air flow was from that point over the top of the bench towards the other parts of the laboratory; in this way all the workers in the same laboratory except the one using the apparatus were aware of and exposed to any vapour leaking from, or inadequately condensed in, the condensers.

For some days the other research workers in the laboratory had remarked on the pungency of the isovaleraldehyde in the atmosphere, while two had complained of some tightness of the chest and weakness. On 1 July 1937 the attention of the workers was drawn to the fact that the amount of aldehyde in the air was too strong for comfort, and instructions were given for the preparation to be discontinued owing to the excessive leakage of isovaleraldehyde from the receivers. Enquiry disclosed that several of the chemists were apparently affected, one having had attacks of asthma induced. The following day two chemists complained of tightness of the chest and marked weakness, while two others had nausea, vomiting and headaches. All (except one who had gone home) of the chemists working in the laboratory were seen by me.

At my request Dr G. N. Burkhardt examined the atmosphere of the laboratory the same day, and although the apparatus had been stopped for some hours with a marked improvement in the atmosphere, isovaleraldehyde was detected quite readily in the air by aspirating it through a solution containing dinitrophenylhydrazine. A precipitate of yellow dinitrophenylhydrazine was obtained from the air in several parts of the laboratory and was particularly copious when the air near the top of the apparatus was examined.

Case notes

Case 1

A research chemist, aged 24 years, had been quite healthy, athletic and well until 27 June 1937, and had actually been medically examined 5 weeks previously. Having been absent from the laboratory he had had only 7 days' exposure to its atmosphere.

On 27 June 1937, he had severe pain across the chest and noticed that he was short of breath, perspired freely, felt weak and short of energy. He had intermittent attacks of dizziness, some vague indigestion with looseness of the bowels, severe irritation of the throat and larynx, and cough, but no headaches, nausea or vomiting.

Examination: pulse 92, regular; blood pressure 135/80. His general nourishment was good; complexion was pale but there was no anaemia. The apex of the heart was not palpated or percussed but appeared to be shifted to the right to the mid-line. The chest moved well and equally, vocal fremitus was normal and equal on both sides. Resonance was duller at the right apex; vocal resonance normal; there was deficient air entry to both apices but no adventitious sounds. The nervous system and abdomen were normal.

Urine: 1018, acid, no sugar, albumin, acetone or casts.

Blood count: R.B.C.'s 5,000,000 per c.mm.; haemoglobin 100%; colour index 1·0; W.B.C.'s, 6000 per c.mm. Differential white cells normal.

Spectroscopic examination of blood and urine did not show any abnormal haemoglobin derivatives.

X-rays of the chest on 2 and 5 July 1937 showed a partial pneumothorax in the left lung field with displacement of the heart and mediastinum towards the right.

On 29 July 1937 Dr Twining reported the lung had completely expanded.

Case 2

A research chemist, aged 22 years, had been working on the preparation of isovaleraldehyde for 2–3 months (the preparation being carried out in the fume cupboard). Two or three weeks previously he had developed a chronic dry cough, with expectoration. He had also had recurrent attacks of pain in the chest, more particularly on coughing, lassitude, anorexia, insomnia and headaches; sweating had also become obvious, especially at night. There was no soreness of throat, loss of weight or gastro-intestinal symptoms.

Examination: very well developed and athletic type; pulse 80, marked sinus arrhythmia; blood pressure 130/85. Tongue and tonsils normal. The heart appeared to be normal but sounds were distant owing to slight emphysema of the lungs which were otherwise normal. Nervous system and abdomen were normal.

Urine: 1016, neutral, no albumin, acetone, sugar, casts, or abnormal pigments (spectroscopically). The blood count was normal, and radiograms of the chest did not show any abnormality.

Case 3

A research chemist, aged 24 years, was quite well until 1 July 1937, when he suddenly complained of dizziness and a feeling of tightness and headache over the frontal region of the head, nausea and the vomiting of bile-stained gastric contents. He had lost his appetite, and had diarrhoea but no indigestion or flatulence. He felt very sleepy, short of energy, but there was no cough. He complained of some scalding pain on micturition which was apparently due to a *B. coli* infection.

Examination: pulse 94, regular, full; blood pressure 135/80. Tongue and tonsils normal. There was some tremor of the hands. Heart, lungs, abdomen, and nervous system were normal.

Urine: 1030, acid reaction; no acetone or albumin; a slight trace of sugar; pus and *B. coli* were present in the centrifuged deposit.

Blood count: R.B.C.'s 4,990,000 per c.mm.; haemoglobin 90%; colour index 0·95; W.B.C.'s 14,000 per c.mm.; polymorphonuclears 70%; lymphocytes 27·5%; large mononuclears 2·5%; no eosinophils or basophils. Slight aniso- and poikilocytosis. No abnormal cells.

Spectroscopic examination did not show the presence of any abnormal haemoglobin derivatives in the urine or blood.

X-ray examination of the chest was normal.

The *B. coli* infection was cleared up completely by treatment with sulphanilamide in 2 weeks.

Case 4

A research chemist, aged 24 years, was well and had been working in the laboratory for 9 months making the same aldehyde.

One week prior to my seeing him he began to notice that he was unusually tired and felt sleepy, was short of energy, and had developed mild diarrhoea, nausea, vomiting and headaches. There was no indigestion, flatulence or pain in the chest.

Examination: pulse, 72, regular; blood pressure 125/80. Tonsils and tongue were normal. The heart, lungs, abdomen and nervous system were normal.

X-ray examination of the chest was normal.

Urine: 1014, alkaline reaction, no albumin, acetone or sugar. The blood count was normal.

Case 5

A research chemist, aged 35 years, was normally healthy but during May to September in the previous 7 years he was liable to severe attacks of hay fever which were readily controlled by ¼ grain of ephedrine orally per day. During the week prior to seeing me, however, he had had considerable difficulty in controlling it with increased doses, even three times daily, and attacks of asthma had also been induced. He developed severe dyspnoea, insomnia and cough with weakness and lack of energy, but there were no gastrointestinal symptoms.

Examination: pulse 96, regular; blood pressure 130/70. Dyspnoea was very marked. Tongue and tonsils were normal. Heart, abdomen and nervous system were normal. There were some rhonchi in the right lung.

Urine: 1016, neutral reaction, no albumin, acetone or sugar.

The blood count was normal. Spectroscopic examination did not show any abnormal haemoglobin derivatives.

X-ray examination of the chest was normal.

Case 6

A research chemist, aged 24 years, was usually fit and well. He had only been in the laboratory for 14 days and not during the 2 weeks prior to the examination by me. He had had symptoms of amyl alcohol poisoning some 5 years previously but did not have a recurrence of these or other symptoms this time.

Examination: pulse 70, regular; blood pressure 130/85.

There was nothing abnormal in the heart, lungs, abdomen or nervous system. Urine: acid reaction, 1014, no acetone, albumin or sugar. An X-ray examination of the chest was negative. The blood count was normal.

Case 7

A research chemist, aged 24 years, was normally fit and well. For 9 months he had been working on the apparatus responsible for the air contamination, preparing isovaleraldehyde from isoamyl-alcohol, without any ill-effects. He did not complain of any symptoms except slight diarrhoea at this time; otherwise, he felt well.

Examination: pulse 78, regular; blood pressure 130/80. The heart, lungs, nervous system and abdomen were normal.

Urine: 1018, alkaline reaction, no albumin, acetone, sugar. An X-ray examination of the chest was normal. The blood count was normal.

None of the cases was very severely affected and all recovered rapidly in a few days without any special treatment after removal from exposure to the isovaleraldehyde.

In this series of cases the first feature was the almost simultaneous appearance of symptoms following more marked contamination of the atmosphere of the laboratory with the pungent-smelling isovaleraldehyde. The onset of the symptoms was similar in all of the cases—a sense of tightness in the chest followed by a cough, together with shortness of breath, and marked loss of energy and weakness. Dizziness and headaches, profuse perspiration, nausea, vomiting and looseness of the bowels occurred in some, but loss of appetite and indigestion were less obvious. Some irritation of the mucous membranes of the pharynx and larynx, and sleepiness were noted in some cases. In case 1,

clinical findings suggested and radiograms disclosed a partial pneumothorax, but no changes were noted in the others. A moderate degree of tachycardia was noted in the patients most affected, but others did not show it, having improved considerably when seen by me a day or two later, owing to their having discontinued work in the laboratory at the commencement of the more severe symptoms. The blood pressures were all within normal limits. No abnormal features were noted in the bloods and urines (except one containing *B. coli*), blood counts were normal and abnormal pigments were not detected spectroscopically.

The variable degree of sensitivity that may be noted in different individuals when exposed to toxic vapour was seen in these patients.

Of the seven patients examined five had symptoms of varying degree, one had slight diarrhoea, and the seventh had no symptoms but he had not been exposed to the laboratory atmosphere for the 2 weeks before examination. Another patient had had symptoms but was not seen by me.

These clinical symptoms resemble those seen after intoxications due to the vapours of other aliphatic aldehydes such as formaldehyde and acetaldehyde, the chief features being irritation of the mucous membranes of the upper respiratory passages; later cough, tightness of the chest, a severe sense of pressure in the head, dyspnoea, weakness, palpitation, tachycardia, profuse perspiration, insomnia or somnolence, anorexia, and in more acute cases nausea and vomiting. Some nervous manifestations and methaemoglobinuria may occur.

Somewhat similar symptoms may follow amyl alcohol intoxication, but in this incident, isovaleraldehyde (b.p. 92–93) and not amyl alcohol (b.p. 131) was very easily detected in the atmosphere chemically, apart from its smell, while the great difference in boiling points could not permit of the appearance of the amyl alcohol in significant quantity during the preparation or refractionation of the isovaleraldehyde.

SUMMARY

The toxic effects of 2-methylbutyraldehyde (isovaleraldehyde), arising from the accidental contamination of a laboratory atmosphere, are described in six out of a group of seven chemists. These were mainly tightness in the chest, irritation of the upper respiratory tract, cough, dyspnoea, marked loss of energy and weakness, dizziness, headaches, profuse perspiration, tachycardia, nausea, vomiting, diarrhoea, anorexia, somnolence, sometimes insomnia, and in one case a partial pneumothorax.

All recovered rapidly when removed from the exciting cause.

I am indebted to the late Dr E. W. Twining for his X-ray examinations of these patients.

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