

A role for trichloroethylene in developing nation anaesthesia

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Developing nations lack the resources that western nations have when it comes to delivering anaesthetics. They deliver the best anaesthetic they can, using the cheapest methods available. Drawover systems for vapour delivery are widespread, and unfortunately, consume large quantities of anaesthetic agent (usually Halothane). This is a considerable expense. Cost savings and improved safety could be delivered by using Trichloroethylene (TCE) in conjunction with Halothane. Unfortunately, production of pharmaceutical grade TCE ceased in 1984, and in some centres industrial grade and reagent grade TCE has been substituted. Samples of industrial grade, reagent grade, and pharmaceutical grade TCE were obtained and analysed to try and validate its use in developing nations, and a case is made for its re-introduction.

The problem in the developing world

Anaesthesia in the developing world and in remote and difficult circumstances is a far cry from western anaesthesia. First world anaesthesia delivers excellent care but at incredible expense. We consume costly drugs, discard single use items, and utilise anaesthetic machines that are not only expensive to purchase but are expensive to maintain. Typical service and maintenance costs of a modern anaesthetic machine are said to be 10% of its purchase price every year.

These sorts of resources are simply not available to anaesthetists in developing countries. Anaesthetic departments there, far from having budgets increased, are being forced to provide more and more services for less and less money in real terms. In 1994 in Malawi, the average cost of anaesthetic drugs and consumables was estimated to be \$US 3.96 per case¹. Compare this to 1st world conditions where this might be the cost of a single anti-emetic given. In Pokhara, Nepal, patients' relatives are asked to buy drugs from the pharmacy and then pass them onto the anaesthetist so that the operation can proceed². Single use items are never single use in the developing world. Needles, syringes, and endotracheal tubes are continually recycled.

One of the main adjustments to provide cheap and safe anaesthesia in the developing world is the

abandonment of plenum anaesthesia and circle systems. As well as being expensive to buy, these machines are costly to maintain, with servicing and spare parts not being readily available. They are not portable and not very robust. Also, they are dependent on a continuous supply of Nitrous Oxide and Oxygen, both to drive the vaporisers and ventilators, and also to prevent hypoxic mixtures from being delivered. This is completely impractical in an environment where bottled oxygen is often not available, the electricity supply is unreliable, and where Nitrous Oxide is too expensive. Before its use was discontinued at The Queen Elizabeth Hospital in Malawi in 1988 Nitrous Oxide accounted for a quarter of the pharmacy budget for the entire hospital!³

To circumvent this problem, draw over anaesthesia is extensively utilised. Using drawover techniques allows the use of atmospheric air as a carrier gas. This is inherently safe as a hypoxic mixture cannot be given. As room air is the carrier gas, greater than 18% inspired oxygen is always delivered (21% oxygen mixed with vapour). Supplemental oxygen can be given at 1 to 4 litres per minute via a T-piece connection to the reservoir tubing. 1 litre/min of supplemental oxygen will deliver an inspired oxygen concentration of 30%.⁴ This is supplied by Oxygen concentrators which can be run for as little as 5 US cents an hour. Thus you can dispense with cylinders, reducing valves, flow metres, humidifiers, and soda lime.⁵ The techniques are simple, cheap, and robust and therefore well suited to developing nations as maintenance costs are greatly reduced.

One of the problems with drawover techniques, however, is that anaesthetic vapours are not recycled, and so volatile use is high. This can present a great financial burden to already strained anaesthetic budgets. Halothane is the most widely used agent in developing nations, and whilst this is incredibly cheap by western standards (being a tenth of the price of Sevoflurane), by developing nation standards it is a considerable expense.

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In a study conducted in 1994 in Malawi, Halothane accounted for a quarter of the entire anaesthetic department budget.³ In another study, Eltringham, using the Glostavent Anaesthetic machine with Halothane as the sole agent, found that the mean use of Halothane was 16mls per hour.⁶ At \$US 35 per 250 ml bottle this works out to be 14 cents per ml, or \$US 2.24 per hour of use. And this study was conducted using supplemental fentanyl for analgesia, a luxury not often afforded in developing nations. Often Halothane is given as the sole agent, with no supplementary analgesia, and thus, deeper anaesthesia would be required, with subsequent increased costs. To put this further into perspective, Halothane can cost several times more than the salary of the person using it.⁷ In Malawi, anaesthesia is usually administered by paramedical anaesthetists, who in 2001 earned 3000 kwacha per month, or \$US 0.30 per hour.⁸ Compare this with the average halothane cost of \$US 2.24 an hour.

Furthermore, as stated earlier, Halothane is often given as the sole agent, with no intra-operative opioids. Since it has no analgesic properties, deeper planes of anaesthesia are required before surgery can be tolerated. This becomes expensive, and potentially unsafe, with an increase in arrhythmias and hypotension.

And so, it is in this context, that a case for Trichloroethylene (a long abandoned agent) can be made, to reduce costs, to improve analgesia, and to deliver safer anaesthesia.

The rise and fall of Trichloroethylene

TCE is a chlorinated hydrocarbon commonly used as an industrial solvent. It is a clear, non-flammable liquid with a sweet smell. Emil Fischer discovered Trichloroethylene while working on the preparation of tetrachloroethylene in 1864. Jackson, in the USA, anaesthetised dogs with TCE in 1936, and Hewer first used it clinically in 1940.⁹

Physical Properties: TCE is a clear, colourless liquid with a molecular weight of 134. It has a boiling point of 86.7 C and a saturated vapour pressure at 20 C of 64.5 mmHg. It is poorly volatile, and it is difficult to achieve greater than 1% output from any vaporiser. It has a MAC value of 0.17%, making it one of the most potent volatile agents described. It has a Blood:Gas partition co-efficient of 9.15. This great solubility in blood means that it takes a long time for brain levels to rise to anaesthetic levels, and also indicates a slow washout time. Pharmaceutical grade TCE was stabilised with 0.01% Thymol. Decomposition occurs in the presence of

strong light and heat (to hydrochloric acid and phosgene), and so it should be stored in tinted glass bottles or metal containers.⁹

Pharmacokinetics: Due to its high blood:gas solubility co-efficient TCE takes a long time to reach levels in the brain sufficient for anaesthesia. TCE is one of the most heavily metabolised of all the volatile agents, 20% of which is metabolised in the liver.¹⁰ It is initially metabolised to Chloral Hydrate, and then either Trichloroacetic acid or Trichloroethanol. Trichloroacetic acid is harmless, but Chloral Hydrate and Trichloroethanol both possess sedative properties, and this is thought to contribute to TCE's post anaesthesia sedation.¹¹ A minor metabolite is also Monochloroacetic Acid, which is toxic. However, only very small quantities are produced and this is not thought to be a problem.⁹

Pharmacodynamics: TCE provides marked analgesia at sub-anaesthetic concentrations. It is difficult to achieve deep planes of anaesthesia with it and it is best suited to light anaesthesia.

Cardiovascularly it is not associated with any appreciable drop in the blood pressure.⁹ Arrhythmias can occur and are typically divided into two categories. On induction increased vagal activity can cause sinus bradycardia, A-V node block, and A-V nodal rhythm. During maintenance, ventricular ectopics, bigeminy, and isolated runs of ventricular tachycardia may occur. Adrenaline can be used with TCE but only cautiously.¹²

From a respiratory point of view, TCE is noted to cause a marked tachypnoea. TCE does not relax the skeletal musculature and muscle relaxants must be employed if surgical relaxation is required.

Toxicity: Shortly after it was introduced as a volatile agent in the 1940's reports of cranial nerve palsies began to surface. It was found that TCE reacted with the soda lime in circle systems. Decomposition of TCE occurs in the presence of sodium and potassium hydroxide, especially at high temperatures. Under these conditions TCE breaks down into Hydrochloric Acid and Dichloroacetylene. This Dichloroacetylene then breaks down to either Phosgene and carbon monoxide, or Dichloroacetyl Chloride and Trichloroacetyl Chloride. These compounds, especially Phosgene, are neurotoxic, and lead to cranial nerve palsies. Most commonly affected is the trigeminal nerve, but also oculomotor, auditory, and facial nerves. Use of TCE in a circle system with CO₂ absorbers is therefore contra-indicated.⁹

Chronic exposure to TCE has been reported to affect the liver, kidneys, immune, and endocrine systems.¹³

Carcinogenicity: The long term effects of TCE as a potential carcinogen are hotly debated. The American Conference of Governmental Industrial Hygienists (ACGIH) has classified TCE as “Carcinogenicity Designation A5: Not suspected as a human carcinogen”. The International Agency for Research on Cancer (IARC) however, has designated TCE as a “group 2A substance: probably carcinogenic to humans”. The U.S. Environmental Protection Agency (EPA) is conducting a re-assessment of the carcinogenic potential of TCE. A report is expected in 2006. The Australian National Health and Safety Commission exposure standards for TCE states that there is inadequate evidence from human studies for the carcinogenicity of TCE.

The 10th Report on Carcinogens, prepared by the U.S. Department of Health and Human Services in 2002 states that TCE is “reasonably anticipated to be a human carcinogen”¹⁴ based on:

- *limited evidence of carcinogenicity from studies in humans.* Occupational exposure to TCE in a meta-analysis of 7 studies showed an increased incidence of cancer of the kidney, liver, and non-hodgkins lymphoma. However, small sample sizes were used and workers were also exposed to other solvents. Other studies have shown no relation at all to cancer.
- *sufficient evidence of carcinogenicity from animal studies.* Tumours have been seen in the same sites as humans.

The purported mechanism of carcinogenicity is thought to be related to TCE’s metabolites. However, TCE and most of its metabolites are not potent geno-toxicants in in-vitro and in-vivo test systems.

From a patient perspective, TCE’s long term safe use as an anaesthetic did not lead to an increased incidence of cancer as compared to background levels, indicating that any such effect is probably extremely low level.

Of greater concern is the possible long term effect on theatre staff if TCE is to be used extensively. The ACGIH has set a threshold limit value (TLV) of 50 ppm. This is the level of exposure that a worker working a 40 hour week can be exposed to without suffering adverse effects. The exposure limit set by the Occupational Safety and Health Administration (OSHA) is 100 ppm. . To put this into perspective,

the current Australian National Health and Safety Commission standard for Nitrous Oxide levels in operating theatres is 25 ppm . This is easily achieved with proper scavenging, and Nitrous Oxide is delivered in concentrations of up to 70% to patients, compared to 0.3 to 1% with TCE. Without the use of scavenging, or inadequate scavenging, TCE exposure to operating room personnel may rise to unacceptable levels.

Clinical Use: Due to its low volatility and high blood:gas solubility co-efficient uptake of TCE is very slow. When used as the sole agent it should be delivered at 1% for approximately 20 minutes (which is usually the maximum that a vaporiser can deliver), despite its MAC value being only 0.17%, before reducing to 0.4 – 0.5%. Because of its high solubility, it should be switched off 20 minutes before the end of a case to allow the agent time to wash out.¹⁵ Of course, as noted earlier, it should never be used in a circle system.

On being introduced in the 1940’s TCE supplanted chloroform and ether due to its decreased cost, reduced hepatotoxicity, non-flammable nature, and lack of respiratory irritation. However, as newer agents became available (most notably Halothane), it lost popularity for many reasons. Despite being very potent, due to its low volatility vapourisers struggled to produce a high enough concentration to produce anaesthesia. Light anaesthesia was possible but attempting deeper planes of anaesthesia led to rapid, shallow breathing, with subsequent hypoxia and hypercapnoea.¹⁰ Coupled with the fact that recovery time for patients was high, arrhythmias were common, and most importantly it could not be used in a circle system due to neurotoxicity, its use dwindled. ICI ceased production in 1984, its product license lapsed in 1988, and the last made bottles had a shelf life until 1989.¹⁶

And so, it became obvious that TCE was quite a lousy drug for use as a sole agent. Why then, should anyone use TCE at all? Because, quite simply, in sub-anaesthetic doses it provides outstanding analgesia, maintains respiratory drive, and is cardiovascularly stable.¹⁰ It is also incredibly cheap. A 4 litre bottle of reagent grade TCE (99.5% TCE) can be sourced for \$US 81.68.¹⁷ This is just over \$US 5 dollars for 250 mls compared to \$US 35 dollars for Halothane. In conjunction with halothane as a second agent, TCE can replace the role of Nitrous Oxide in a safe and cost effective manner, whilst also contributing to post-operative analgesia.

Using Halothane and Trichloroethylene together

The use of TCE with Halothane is theoretically advantageous as they are complementary agents. Halothane provides the deeper, more quickly controlled anaesthesia that TCE cannot. TCE provides the intra-operative and post operative analgesia that Halothane lacks. TCE produces tachypnoea as opposed to the slowing of the respiratory rate seen with Halothane. TCE provides cardiovascular stability and reduces the need for the cardiovascular depressant halothane. This leads to significant cost savings and also safer anaesthesia. And so, it is unsurprising that the combination of the two agents has been well described in the literature since at least 1966.¹⁸ Cross contamination of vapourisers is inevitable in any 2 vapouriser system but this does not seem to be a problem with TCE and Halothane. ICI (the suppliers of pharmaceutical grade TCE) have stated that to the best of their knowledge the resultant mixture of Halothane and TCE does not form toxic compounds nor does the mixing of the vapours produce any harmful effects.¹⁹ Multiple techniques for vapour delivery have been published.

The simplest way of delivering TCE with Halothane is to place the TCE in a Goldman vapouriser within the circuit, before the halothane vaporizer. The Goldman vapouriser is a very simple splitting device with low resistance and therefore works well as a vapouriser-in-circuit. It has three active positions via a lever or clicking device. It can be set to 1, 2, or ON (maximum output). It is not agent specific. It has no temperature compensation and output varies with temperature. Typically it falls as the temperature drops during use due to latent heat of vapourisation.²⁰ This is not as big a problem with TCE as it is poorly volatile and so less cooling occurs. Goldmans can be used in spontaneously ventilating or IPPV modes, although plenum use is not recommended due to highly variable output. Also, tipping the vapouriser can spill liquid volatile into the circuit, which is very dangerous, and so a stable base for it is required. The British Oxygen Corporation Reference Card for the Goldman Vapouriser states that at 20 C the vaporiser output for TCE varies as follows:

Drum Position	2 Litres/min	8 Litres/min	30 Litres/min
1	0.1%	0.1%	0.1%
2	0.2%	0.5%	0.5%
ON	0.5%	1.0%	0.5%

Thus, the maximum theoretical output for TCE is 1.0% in the ON position at 8 Litres/min. This is

probably a tad generous as Fentons work in Malawi shows that maximum output from a Goldman in the ON position (with gauzes soaked in the Goldman bowl to increase surface area) for TCE is approximately 0.7%.¹⁶ Yaddanapudi and Kaul in 1993 analysed Goldman outputs using Raman Spectroscopic evaluation and found that the output of Halothane at 6 Litres/min in the ON position was 2.15%, which is lower than the stated output of 2.5% on the reference card.²¹ Thus, the actual maximum output with a Goldman is likely to be less than 1.0% and closer to 0.7%. Whilst not a particularly high output, it does ensure safe use as overdose is almost impossible unless the liquid volatile is tipped into the circuit. For longer cases the Goldman is set at ON initially and after 15 minutes reduced to the 1 or possibly 2 lever position. It thus provides background analgesia whilst anaesthetic depth can be altered using Halothane.¹⁶ For short cases it is also very useful as it speeds up an inhalational induction with Halothane by having the Goldman with the TCE in the ON position and the Halothane set at 3%. This pleasant smelling combination works very well and has few adverse effects (Fenton P.M.: personal communication).

The Datex Ohmeda Portable Anaesthesia Complete Vaporiser (PAC) is a multi-agent drawover vaporiser that is effectively temperature compensated using a bimetallic strip. It is for drawover mode only as plenum use leads to unpredictable outputs. Output is not accurate at small tidal volumes and so it is not recommended for paediatric use. It is the field vapouriser for the US. forces and is also used in Malawi.²² Unfortunately, the Universal PAC may not be available with a TCE disk to indicate output in various positions. If TCE was to be used with the PAC then maximum output would have to be estimated at 1.0%.

The Oxford Miniature Vapouriser (OMV) is a portable, robust, versatile multi-agent vapouriser and was probably the most popular vapouriser for delivering TCE. The OMV is reasonably accurate over a wide range of flow rates and tidal volumes, including small tidal volumes. Thus it can be used for paediatrics.²³ Temperature compensation is non-existent but a glycol heat sink buffers temperature changes. Despite the lack of temperature compensation Prior found that between 18 – 30 C the output of the OMV with TCE varied less than 0.1%.¹⁵ However, output falls dramatically at less than 15 C and rises steeply at greater than 35 C. OMV's are multi-agent and simply require a change of agent disk on the controls according to the agent of choice. Maximum output with TCE is 1.0%. 2 OMV's can

be linked in series to form the Triservice apparatus. The Triservice apparatus is the field vapouriser for the Australian Defence Forces. Currently both vapourisers are filled with Isoflurane to augment output, but originally it was designed to have TCE in the first vaporiser and Halothane in the second (closest to the patient), and was used successfully for many years. If no TCE disks are available then simple labels can be made and marked according to the many photographs of Filene OMV disks that have been published. Tighe, in 1987, compared Halothane and TCE in a Triservice apparatus with Isoflurane using one OMV.²³ 48 servicemen presenting for minor orthopaedic or general surgical operations were randomised to receive a spontaneously ventilating technique using either the TCE/Halothane combination or Isoflurane. Despite the more favourable pharmacokinetic profile of Isoflurane the results showed little clinical difference between the two techniques. The results were as follows:

	Halothane/TCE	Isoflurane
Mean induction time	6.8 minutes	6.2 minutes
Mean operative time	25 minutes	26 minutes
Mean anaesthetic time	40 minutes	42 minutes
Mean recovery time	16.4 minutes	18.2 minutes

In the key areas of induction time and recovery time, it can be seen that the two groups produced essentially equal results. From a pharmacodynamic perspective there was no statistical difference between the two groups with regards to Blood Pressure, End Tidal CO₂, Tidal Volumes, or Minute Volumes. The Halothane/TCE combination did result in a higher respiratory rate (30 breaths/min vs. 20 breaths/min) and a slower heart rate compared to Isoflurane. Thus, it can be seen that a combination of Halothane and TCE in a Triservice setup is just as effective as a modern agent, Isoflurane, but at greatly reduced cost.

Hollis, in 1987, investigated the possibility of mixing Halothane and TCE together in a single OMV.²⁴ A mixture of 3 parts Halothane to 1 part TCE was used. Halothane and TCE when mixed together in the same vapouriser do not react chemically with each other. Unfortunately, they do not form an azeotrope. This means that they do not mix together to form a solution that has one boiling point and hence one

saturated vapour pressure (unlike ether mixed with halothane). The mixture behaves as two separate agents, each with its own vapour pressure. The upshot of this is that the proportions of Halothane to TCE change continuously as they are vapourised. Hollis found that Halothane output tended to fall over time and TCE output rose over time. At the 70 degree setting on the OMV Halothane output dropped over one hour from 2.0% to 1.4%, and TCE output rose from 0.5% to 0.7%. In clinical use (albeit with only 4 patients) Hollis did not believe that the output changes were of significance to the anaesthetic, and he concluded that if only one OMV vaporiser was available then it was an acceptable and safe technique, and certainly better than Halothane on its own. Mixing of Halothane and TCE in a single vaporiser could theoretically be applied to any multi-agent vaporiser, but this has never been formally tested.

Analysis of Trichloroethylene samples

The problem, of course, is that TCE no longer exists. Not pharmaceutical grade anyway. ICI ceased production in 1984. However, in Malawi they have been using industrial and reagent grade TCE since 1986. It is also used in Nepal. It has proved very useful both as a cost saving measure and also as a way of providing safer anaesthesia when used in conjunction with Halothane. In Malawi at least, 15 years of clinical use has not resulted in any unexpected adverse effects (Fenton PM: personal communication). Despite this, however, the fact remains that their use of non-pharmaceutical grade TCE whilst apparently safe, has never been validated. What exactly is in industrial and reagent grade TCE besides the trichloroethylene? And is it safe to use?

Answers to these questions were sought by obtaining samples of industrial and reagent grade TCE from Malawi and Nepal that had been used for anaesthesia, analysing them, and comparing them to British Pharmaceutical grade TCE (Trilene). The details of the three details were:

1. Trichloroethylene (Reagent Grade) in Qualigens Fine Chemicals bottle from Kathmandu in Nepal (imported from India).
2. Trichloroethylene (Industrial Grade) in "Isoflurane" bottle, dry cleaning fluid from Malawi.
3. Trichloroethylene (BP Grade) in Trilene bottle.

The samples were analysed in the laboratories of Forensic Science Service Tasmania (Australia). Analysis was by Gas Chromatography using Flame

Ionisation Detection (GC/FID) and Mass Spectrometric Detection (GC/MS). The trichloroethylene purity was estimated to be greater than 98% for all three bottles. The reagent and industrial grades of TCE were no less pure than the pharmaceutical grade. As well as TCE, several additional compounds were found in the samples.²⁵

1. Reagent Grade TCE: tetrachloroethylene, 1,1,2-trichloroethane, 1,3-dichloro-2-propanol, phenol, dichloroethylene, chloroform.

2. Industrial Grade TCE: tetrachloroethylene, 1,1,2-trichloroethane, methylchloroacetate, bisphenol A, isoflurane (from bottle?), dichloroethylene, chloroform.

3. Pharmaceutical Grade TCE: : tetrachloroethylene, 1,1,2-trichloroethane, diethylcarbamyl chloride, thymol, triphenyl phosphate.

It should be remembered that for each sample these additional impurities comprised less than 2% in total. However, to validate the technique of using non-pharmaceutical grade TCE in anaesthesia it is necessary to investigate the acute effects of these compounds on patients, the potential chronic effects of them on theatre personnel, and the likely levels during normal use to which they will be exposed.

Tetrachloroethylene: TCE is produced by combining dichloroethane with chlorine. The reaction produces trichloroethylene and tetrachloroethylene and these are then separated by distillation. It is unsurprising therefore that tetrachloroethylene is present in all three samples.

Acute Effects: Can cause irritation of the skin, eyes, and respiratory tract. Occasional effects on kidney and liver function have been noted.

Chronic Effects: Chronic exposure may affect the liver and kidneys.²⁶

Carcinogenicity: Studies assessing the carcinogenicity of tetrachloroethane have shown conflicting evidence. The IARC currently finds sufficient evidence to designate tetrachloroethylene as carcinogenic in animals, with limited evidence in humans. However, Mundt, in a critical review of the epidemiological literature published in September 2003 found that “the current epidemiological evidence does not support a conclusion that occupational exposure to tetrachloroethylene is a risk factor for cancer of any specific site”.²⁷

Conclusions: The acute effects do not seem to be a concern. Regarding the safety of theatre personnel, the ACGIH TLV for tetrachloroethylene is currently

25 ppm. With a saturated vapour pressure of 14mmHg at 20 C (a quarter of TCE's), and at the levels present in the TCE samples, the exposure level to the patient is at most 45 ppm. Theatre exposure levels are likely to be significantly lower than this, and especially if scavenging is used.

1,1,2-Trichloroethane: 1,1,2-Trichloroethane is used as a chemical intermediate and as a solvent. It was present in all three samples.

Acute Effects: No information is available for the acute effects of inhalation of 1,1,2-Trichloroethane in humans. Animal studies have reported effects on the liver, kidneys, and CNS.²⁸

Chronic Effects: No information from human studies is available. In animal studies, no long term effects were seen.

Carcinogenicity: The IARC in 1999 stated that 1,1,2-Trichloroethane was not classifiable as to its carcinogenicity to humans as there is no data available from human studies. There is limited evidence for the carcinogenicity of 1,1,2-Trichloroethane in animals.²⁹ The U.S. EPA has classified it as “Group C, possible carcinogen”.

Conclusions: The ACGIH TLV, NIOSH recommended exposure limit, and OSHA permissible exposure limit for 1,1,2-Trichloroethane is 8 ppm. Patients are likely to be exposed to more than this for short periods of time but staff are unlikely to encounter unsafe levels. Based on the known data, it is unlikely that this compound poses any significant danger to either patients or staff.

1,3-Dichloro-2-propanol: 1,3-Dichloro-2-propanol is a compound typically found in soy sauce and oyster sauce. It was present in the reagent grade sample. Its boiling point is 174 C and so it is unlikely that much will be vaporised at 20 C. There is no data available on inhalational toxicity, only toxicity by ingestion. Chronic exposure can lead to hepatotoxicity and kidney impairment, but only at doses far in excess to those found in the TCE sample. It is unlikely to cause any adverse effects to patients or staff.^{30 31 32}

Phenol: Phenol was present as an impurity in the reagent grade sample. Phenol is highly toxic and acute effects include corrosion of mucosal surfaces, pneumonitis, pulmonary oedema, and cardiorespiratory arrest. Chronic exposure may affect the liver and kidneys. However, its boiling is 182 C and its saturated vapour pressure at 20 C is 0.24 mmHg. At the level present in the sample and with its high boiling point, exposure to the patient is approximately 5 ppm, which does not exceed the ACGIH 2004 occupational exposure limit. Staff are

exposed to even lower levels, and so phenol exposure is unlikely to cause adverse effects.

Dichloroethylene: Dichloroethylene was present in the reagent grade sample.

Acute Effects: Can cause eye and respiratory tract irritation and depression of consciousness.

Chronic Effects: Dichloroethylene may have effects on the liver.

Carcinogenicity: No studies have been done to investigate carcinogenicity in animals or humans.

Conclusions: The ACGIH TLV for dichloroethylene is 200 ppm, which is a far greater concentration than that to which patients or staff would be exposed. Dichloroethylene is unlikely to have any adverse effects.^{33 34 35}

Chloroform: Chloroform was present in trace amounts in the reagent and industrial grade samples. At these levels this well known agent will not cause adverse effects.

Methyldichloroacetate: Methyldichloroacetate was found in the industrial grade sample. There is very little published literature on this compound. No exposure limits have been set but the Material Safety Data Sheet published by a methyldichloroacetate supplier states that it causes burns, is a respiratory irritant, and that inhalation may be fatal.³⁶ At what dose this occurs is unpublished, and the lack of exposure limits raises concerns about what a safe level of exposure would be. Despite the fact that clinical use of industrial grade TCE in Malawi showed no unexpected adverse events, in particular pneumonitis (Fenton PM: personal communication), this is of concern.

Bisphenol A: Bisphenol A was found in the industrial grade sample. Its boiling point is 250 C and so its vaporisation at 20 C is negligible. Acutely it may cause respiratory irritation. No chronic exposure effects have been documented. It is not carcinogenic. No exposure limits have been established. It is not of concern to patients or staff.^{37 38}

Diethyl Carbamic Chloride: Diethyl carbamic chloride is an intermediate used in the production of pharmaceuticals, and was found in the pharmaceutical grade TCE. Little published information is available. In high enough doses it can cause respiratory tract irritation and even a pneumonitis. However, TCE's longstanding use as an anaesthetic agent without reports of pulmonary difficulties indicate that the amounts present are too small to pose a concern to staff or patients.^{39 40}

Triphenyl Phosphate: Triphenyl Phosphate was found in the pharmaceutical grade TCE. Its boiling point is 370 C and so at 20 C evaporation is negligible. Long term exposure may have effects on the peripheral nervous system. Again, this has not been reported with TCE use (outside a circle system), and so the levels must be extremely low.⁴¹

All three samples contain multiple compounds as impurities. Regarding the pharmaceutical grade TCE, despite the fact that potentially toxic compounds are present, their levels are obviously low enough so as not to cause problems, as there is little published information to suggest otherwise. In the industrial grade and reagent grade samples, the compounds detected were mostly of minor concern to patients. Respiratory tract irritation and potential short term effects on kidney and liver function may be seen. Exposure levels to staff, especially with adequate scavenging, are likely to be of minimal concern. Of more concern, however, is the presence of Methyldichloroacetate in the industrial grade sample. Whilst undoubtedly present in low levels the lack of a known safe exposure limit is worrisome.

Discussion

TCE deserves to be reconsidered for widespread use in developing nations. In the niche area of under-resourced countries relying on drawover anaesthesia it possesses qualities that are quite advantageous.

TCE in conjunction with Halothane would improve the safety of the anaesthesia delivered to patients. Halothane is a very potent anaesthetic agent, and without agent monitoring and supplemental analgesia, the deep anaesthesia required to allow surgery can lead to patient morbidity. TCE is cardiovascularly stable and would reduce halothane use by a third, and thus improve safety. Due to its low volatility TCE is an inherently safe agent as so little of it can be vaporised. Arrhythmias do not seem to pose a significant problem, in Malawi anyway, because the incidence of heart disease in the population is low.

In areas where resources are extremely scarce, often patients are given no peri-operative opioids. TCE provides excellent analgesia intra-operatively, and this can extend for several hours into the post-operative period.

Finally, TCE is incredibly cheap and would provide significant cost savings in countries where Halothane use is the major expense in anaesthetic budgets. Reagent grade TCE can be sourced for \$U.S. 5.00

dollars for 250 mls. This works out to be 2 cents per ml. Due to its low volatility very little of it is used. Using the Triservice apparatus Tighe found the average TCE usage was 5mls/hr. This works out to be 10 cents per hour when used with Halothane. Halothane use was 22mls/hr, at a cost of \$3.20 an hour.²⁴ Assuming that TCE would cut Halothane usage by a third, this would provide a net cost saving of approximately \$U.S. 1.50 an hour. By developing nation standards this is an enormous saving, which could be channelled back into capital expenditure, improved training, and the ability to offer increased services.

TCE is also relatively easy to administer. Delivery can be via a Goldman vapouriser, an OMV, Triservice apparatus, PAC vapouriser, and even mixed together with Halothane as a single solution.

Analysis of the industrial, reagent, and pharmaceutical grade samples of TCE showed that they were all greater than 98% pure TCE. All contained impurities, even the pharmaceutical grade. Analysis of the impurities showed that at the concentrations likely to be delivered to patients and staff most of them are no more harmful than the TCE itself. Of concern, however, was the methylchloroacetate found in the industrial grade sample. Until more is known about safe exposure levels of this compound it cannot be recommended for use. Industrial grade TCE is available for \$U.S. 3.75 for 250mls. At only slightly increased cost (\$U.S. 5.00 dollars for 250 mls), reagent grade TCE can be obtained which is greater than 99.5% pure TCE. This is as pure, or purer, than pharmaceutical grade TCE.

In a perfect world, of course, ease of mind would be guaranteed by the reintroduction of pharmaceutical grade TCE. This is most unlikely to ever happen. TCE production was ceased in 1984 due to a lack of profitability. It is unlikely that any pharmaceutical company is going to commit resources to producing a drug that can only be used in the small market of drawover systems, and which provides a profit which is paltry compared to modern volatile agents. And so, the question is raised, is it ethical to encourage anaesthetists to use a drug that is not licensed for use in humans? When the difference between pharmaceutical grade TCE and reagent grade TCE goes no deeper than the label on the bottle, the answer is almost certainly yes. Especially when the agent has such a potentially positive role to play in reducing costs, providing analgesia, and improving patient safety. Furthermore, TCE has been used safely since the 1940's. Whilst being a poor single

agent, very few concerns have been raised about its safety outside of circle systems. An analogous situation in the western world would be the off-license usage of drugs that occur in anaesthesia on a daily basis. Very few drugs are licensed for use on young children or pregnant women, and yet, every day we administer them because there is no evidence to say that we shouldn't, and we know that the sole reason for the license not being extended is the pharmaceutical companies' reluctance to spend millions of dollars on further testing in these small markets. The reality of the situation in the developing world is that drugs and equipment are frequently used in a manner that is against the manufacturers instructions. Whilst it seems unsafe practise in the west to re-use spinal needles, in some countries the choices are stark. Either the needles are re-used or only one person receives an anaesthetic and many miss out. Options are often luxuries that are afforded to richer countries only. In this context then, the use of reagent grade TCE, which is just as pure as pharmaceutical grade TCE, should not be discouraged.

Whilst it has been shown that reagent grade TCE is safe, available, cheap, and easy to administer, the real problem may lie deeper than this. Most anaesthetists in developing nations will have never used it and may be hesitant to do so. They may feel that it is an agent whose time has come and gone and that attempting to re-introduce it would be a step backwards. This is a question that the people using it have to answer for themselves. To avoid using a drug simply because it is old makes little sense. Field hospitals in the armed forces use drawover systems and simple, robust vaporisers, despite the fact that more expensive equipment and drugs would be used in their base hospitals. This is not to save money, but rather because conditions in the field demand simple, portable, reliable, and robust systems. When conditions in developing nations improve, then it would make sense to look at more expensive equipment and drugs. However, in the situation as it stands, the re-introduction of TCE would seem a logical and progressive idea, improving patient safety and delivering cost savings that would be of enormous benefit.

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