Controversial topics

Chlorpropamide-alcohol flush: a critical reappraisal

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Chlorpropamide was released for clinical use in 1958 and within a year Signorelli [1], among others, reported: '... the unusual side-effect associated with the ingestion of alcohol during chlorpropamide therapy ... 8 of 23 patients ... complained that after meals they experienced one or more of a number of disagreeable symptoms that consisted of sensations of warmth, flushing, nausea, giddiness and, in some, tachycardia'. However, these disagreeable symptoms were outweighed by the drug's therapeutic benefits, and it has remained in use.

In 1962 Truitt et al. [2] suggested that the chlorpropamide-alcohol flush (CPAF) might be safer than disulfiram in the treatment of alcoholism. Thus already, CPAF was under consideration as a clinical tool rather than an undesirable side-effect.

In 1978 interest in CPAF was rekindled by Leslie and Pyke [3], who in this and subsequent papers [4–8] suggested that CPAF was: (1) dominantly inherited; (2) a possible marker for at least one type of maturity-onset diabetes mellitus; (3) a possible marker of a lesser tendency to develop some micro- and macrovascular complications of diabetes; and (4) a key towards understanding both the aetiology of some forms of Type 2 (non-insulin-dependent) diabetes and the mechanism of this type of flushing.

Before discussing these exciting possibilities, it is important to consider precisely what is understood by CPAF. Chambers Twentieth Century Dictionary [9] states that 'flush, *noun*' is 'a sudden flow; a flow of blood to the skin, causing redness; a suffusion of colour, especially red; *verb, intransitive* to glow; to become red in the face; *verb, transitive*, to cause to glow; to elate, excite the spirits of'. The main features of a flush can therefore be categorised as the subject's symptoms, and changes in cutaneous colour, blood flow or temperature.

Initially the symptom of warmth (reported by questionnaire or in person) was used to determine CPAF status [3]. If symptoms are used in this way, they must be reproducible (i.e. the patients, when given chlorpropamide, must consistently report warmth after alcohol

or remain consistently asymptomatic). Such consistency was found in six patients by Leslie and Pyke [3]. However, Jefferys and Strakosch [10] used a questionnaire with inbuilt 'distractors' to assess symptoms (after a 'do it yourself' test kit of chlorpropamide tablets and sherry), and found that after a single test 11% of patients were unsure of their symptoms. Forty-nine Oxford diabetic patients on long-term chlorpropamide treatment were asked directly, in writing and verbally, about alcohol flushing (if any) at home, and also about symptoms after a supervised standard drink of ethanol. Twenty-one percent gave different answers on different occasions. Furthermore, of five patients twice given the same drink under closely similar conditions, two patients who were at first asymptomatic reported facial warmth the second time [11]. Thus symptomatology is not a completely reliable method of assessing CPAF status, if this is to be considered a permanent condition.

Visible flushing is subject to observer bias and very difficult to quantify, whereas temperature measurement provides a more objective method of assessing flushing, and has often been used [8, 10, 12–20]. However, temperature changes should be clearly and repeatably separable, if CPAF-positive and CPAF-negative patients are to be unequivocally identified. Barnett et al. [14] found that, with patients who had taken 250 mg chlorpropamide daily for 2 weeks, those with symptoms of warmth in a previous test had cheek temperature rises above 1.0 °C, while those previously asymptomatic showed smaller increases. However, Hillson et al. [12] found that cheek temperature rise was continuously distributed in patients on 100–750 mg daily for more than 6 months, and on each dosage considered separately. Furthermore, Hillson et al. [12], Köbberling et al. [17] and Wilkin [21] have all demonstrated that cheek temperature rise after ethanol is determined by the initial cheek temperature among other factors. Early studies at King's College Hospital, London declared there was 'no correlation between the increase in skin temperature and the basal skin temperature' [8], but one was found subsequently [19]. There was no bimodality of basal

cheek temperature in patients on long-term chlorpropamide therapy studied in Oxford [11] or in patients given single doses of chlorpropamide or placebo in Germany [17]. Interestingly, diabetic patients on long-term chlorpropamide therapy, but no other drugs, had lower basal cheek temperatures than diabetic patients on diet alone ($p=0.011$) [11].

Limitations on the maximum possible cheek temperature response to a flushing agent explain at least partly the importance of the starting temperature. The cheek cannot be hotter than the core unless the skin is more actively producing heat than the deeper tissues, and its temperature is limited by, inter alia, the diameter, number and distribution of cutaneous blood vessels, blood flow, and tissue and air heat conduction. Wilkin [21] developed a previous formula [22] to derive a 'malar thermal circulation index' incorporating cheek, sublingual and ambient temperatures both initially and at the height of the temperature rise. However, even such sophisticated calculations are limited, in that neither initial cheek temperature nor cheek temperature response are repeatable despite careful attention to test conditions [11, 17]. Ambient temperature and initial cheek temperature among different patients studied at a room temperature of $20 \pm 0.3^\circ\text{C}$ are not correlated [12], although a correlation was found in men studied over a wider range of ambient temperature [23]. However, even small changes in the temperature at which a given individual is studied may alter the initial cheek temperature [11]; strict control of ambient temperature is expensive and difficult to achieve, and has not been used in most CPAF studies.

Cardonnet et al. in 1959 [24] observed that reduction in the dose of chlorpropamide abolished the flush, and an Oxford patient confirmed this. Plasma chlorpropamide concentration correlates with cheek temperature rise but not with basal cheek temperature in diabetic patients on long-term chlorpropamide therapy [12], and is greater in patients positive for CPAF (the exact procedure used is uncertain) [25]. It also correlates with the 'malar thermal circulation index' [11]. Plasma chlorpropamide concentrations are low in patients who have received only a single dose of chlorpropamide [26], and probably insufficient to promote CPAF, though they certainly would not inhibit an alcohol flush. Barnett et al. [14] suggest that long-term chlorpropamide is required to ensure a measurable CPAF reaction. One must ask though, "In whom?", and remember that Keen et al. [27] could convert CPAF negativity to positivity by sustained chlorpropamide treatment, presumably via the link with the chlorpropamide concentration.

Thus, the apparently simple test of asking the patient about his sensations after one or two tablets of chlorpropamide and a glass of sherry is not adequate to determine CPAF status. Furthermore, even with cheek temperature change as the criterion, both basal cheek temperature and plasma chlorpropamide concentration

need to be considered. Theoretically each test should be performed at the same basal cheek temperature and chlorpropamide concentration. As this is impossible to achieve, both factors should be measured and allowed for in assessing the results.

So what of the original observations which prompted the recent upsurge of interest in CPAF?

The genetics of CPAF

The evidence for dominant inheritance of CPAF [3] is based on symptomatic assessment after the rather misleadingly named *single* challenge test in which patients receive placebo once and 250 mg chlorpropamide once, each followed 12 and 36 h later by 40 ml sherry. Subsequently Leslie and Pyke [28] stated that 86% of 291 patients in their retinopathy study were on regular daily chlorpropamide treatment [5], and were just given sherry while receiving their usual chlorpropamide treatment. It is unclear whether any such patient was included in the genetic studies, which strongly suggested that symptomatic CPAF was dominantly inherited. However, factors such as discussion of symptoms among family members, environmental conditions (e.g. the ambient temperature in the home), and the usual treatment of the diabetic patient should be considered (for example, how many parents of propositi were diabetic, and how many such diabetic parents were treated with chlorpropamide?).

CPAF and Type 2 diabetes

Much of the interest in CPAF lies in the suggestion by Pyke and Leslie [4] that one-fifth of all Type 2 diabetic patients have diabetes inherited as an autosomal dominant and associated with CPAF. They state that 'when offspring of diabetics in whom the disease was diagnosed early were studied, CPAF seemed to precede the appearance of diabetes'. Again, evidence to support these assertions comes from studies of CPAF after the single challenge test [3, 4]. As discussed previously, it is not known how many (if any) of these patients were already receiving chlorpropamide. Of 234 Type 2 diabetic patients tested, 91 had a first-degree family history of diabetes, and 74 (81%) of them reported CPAF, while only 31% of those without first-degree family history (but who may have had second-degree relatives with diabetes) reported CPAF. The total incidence of CPAF was 51% [3]. This figure has been challenged by others [10, 16, 17] as being excessively high. However, 65% of patients on long-term chlorpropamide in Oxford reported facial warmth on ethanol testing [12], in contrast to the 20% of those on diet or other oral hypoglycaemic drugs who did so after a single dose of 500 mg chlorpropamide, but not after placebo [11]. Applying these

figures to Leslie and Pyke's data [3], and assuming 86% of their patients to be chlorpropamide-treated, one can calculate a prevalence of symptomatic CPAF of 59% – similar to that reported. Thus, it seems likely that the majority of the patients in [3] were on long-term chlorpropamide treatment. Older patients especially might well be on chlorpropamide rather than a newer sulphonylurea, and would also be more likely to know of a first-degree family history of diabetes. The incidence of CPAF in Type 1 (insulin-dependent) diabetes mirrors that of alcohol flushing in a Caucasoid community [29], but this possibility was presumably eliminated by using the placebo test. The placebo test is very important in this context, as alcohol flushing is dominantly inherited (among oriental communities) [29].

The association between the apparently dominantly inherited CPAF and a first-degree diabetic family history suggested a link with the dominantly inherited 'Mason-type diabetes or maturity-onset diabetes of youth' (MODY). However, as above, it appeared that CPAF was linked with family history rather than age of onset of diabetes. Thus, in 15 *propositi* diagnosed aged <30 years, all had CPAF, while 16 out of 18 of their diabetic relatives, but only two out of 14 non-diabetic relatives, did so. In those diagnosed >30 years of age, 32 of 37 *propositi* and 17 of 20 diabetic relatives flushed, while none of the non-diabetic subjects did so. Again, it would be helpful to know whether any of these were on long-term chlorpropamide and, if so, whether they had flushed after alcohol before starting that treatment. It is unlikely that any non-diabetic subject was taking chlorpropamide routinely, and symptomatic flushing with alcohol is less likely to occur after a single dose of chlorpropamide than on long-term treatment [11, 27].

Köbberling et al. [17] showed that four of seven patients (treatment not stated) with MODY had CPAF, but that it was absent in another MODY family. Fajans (cited by Harris and Leslie [30]) found that 11 of 19 MODY patients (58%) on long-term chlorpropamide reported CPAF. Dreyer et al. [31] found three of four MODY patients to be CPAF-negative (using the single challenge test), whereas five of 12 Type 1 diabetic patients did flush. Neither de Silva et al. [16], Köbberling et al. [17] nor Radder et al. [18] confirmed the association of first-degree family history of diabetes and CPAF. So far no prospective study of glucose tolerance has been reported in CPAF-positive or -negative non-diabetic patients with a first degree positive family history of diabetes. Soler and Motl [32] reported a single case of a non-diabetic man with CPAF during chlorpropamide treatment for diabetes insipidus, who subsequently developed diabetes mellitus.

Until age and treatment of diabetes are included in analysis of objective testing of CPAF in a large number of patients, the case for CPAF as a phenotype associated with a genetic propensity to Type 2 diabetes must remain unproven.

Liability to diabetic tissue damage

The notion of CPAF as an all-or-none factor was repeated in its 'intra-diabetic' epidemiology. A single determination categorises the patient for life and there is no consideration of CPAF as a property that might be affected, for example, by age, essential hypertension, the development of neuropathy or angiopathy among diabetic patients, or the menopause (though elderly ladies occasionally note a return of post-menopausal flushes unrelated to alcohol after prescription of a substantial dose of chlorpropamides, personal observation). There has not been time for a cohort study on diabetic patients to see whether CPAF status remains constant as tissue damage develops, and yet after 'cross-sectional' studies [5–7] from King's College Hospital, London, it was declared that CPAF-positive patients were less liable to diabetic retinopathy, nephropathy and macroangiopathy than CPAF-negative subjects. For example [5], because of the "almost invariable presence of CPAF in 'Mason-type' diabetics" [4, 33] and their comparative freedom from retinopathy, 291 Type 2 diabetic patients were selected randomly from the clinic except for a special effort to test those diagnosed diabetic >15 years previously (of whom at least 75% cooperated). What happened can only be reconstructed with the help of a later publication [28]. Although 'patients were given a single challenge test' [5], this was actually administered to only 14% [28], as the remaining 86% were already on treatment with chlorpropamide and 'were just given the sherry' (at an unspecified time). If Mason-type diabetes and long-standing Type 2 diabetes are associated at King's College Hospital with treatment with chlorpropamide, one can see that this protocol gave little scope for recognition of flushing from alcohol alone. However, the findings are not unexpected, if recognition of retinopathy in non-insulin-treated patients increased the likelihood of advising prescription of insulin, and if in addition the King's College Hospital clinic has an unusually large proportion of Mason-type patients (and if they are indeed relatively spared from retinopathy, though Fajans would qualify this [34]). One needs to know the CPAF and fundal status of the clinic's insulin-treated Type 2 diabetic patients. A King's study of Type 1 diabetes also showed CPAF relatively dissociated from microvascular damage [35].

The association of CPAF with freedom from retinopathy was supported by Radder et al. [18], but others could not confirm it [31, 36–39]. The postulated link between CPAF and macroangiopathy [6] was supported in a report [40] that also linked CPAF with neuropathy, but again others found differently [37, 39]. Throughout their considerations of tissue damage, the King's group always treat hyperglycaemia as another 'all or none' property [5] and have not incorporated its degree in their analyses.

Mechanisms

How flushing occurs is not well understood, discussion ranging from the detailed debates surrounding the exact contributors to the carcinoid flush [41] to the silent puzzlement in face of post-menopausal flushing, all excellently discussed in two recent reviews [42, 43]. The early suggestion that chlorpropamide acts like disulfiram in increasing the accumulation of acetaldehyde after intake of ethanol [2] has been strongly supported by the clear-cut results from Malmö [15, 44], which showed a threefold-greater increase in plasma acetaldehyde in CPAF-positive than in CPAF-negative subjects. Jerntorp et al. suggested [15] that (a) chlorpropamide inhibits aldehyde dehydrogenase, as already reported [45], and (b) the flush occurred when the acetaldehyde concentration was particularly high after alcohol because of an inherited enzymatic variation, in either alcohol dehydrogenase or aldehyde dehydrogenase. Their basic observation was confirmed from King's [14].

It has long been known that Orientals are particularly liable to flush after ethanol [29] and it is equally true that they flush strongly after ethanol following previous chlorpropamide. However, the flush with placebo chlorpropamide is likely to be so great that they might strictly be recorded as CPAF-negative in the '4-dose' 'single challenge test', providing the placebo part of that was indeed done [3]. Their intense flushing has been suggested to depend upon iso-enzymes of hepatic alcohol dehydrogenase [46], but a recent report from Malmö [47] seeks to implicate erythrocyte aldehyde dehydrogenase in Aryans. Fixed proportions of blood cells and plasma from each subject were homogenised, and homogenate was incubated with acetaldehyde (and the suitable nicotino-pyrimidine nucleotide). Samples were obtained from 20 subjects; none was chronically treated with chlorpropamide, and half were CPAF-positive to ethanol 12 h after a single dose of 250 mg chlorpropamide (no placebo run was undertaken; of the seven men, only two flushed). There was no difference between the homogenates from positive and negative subjects in the acetaldehyde concentration for half an hour after adding the substrate. Thereafter the acetaldehyde concentration was greater in the homogenates from 'flushers'. It is not yet clear whether the 30-min incubation, the fall from an initial substrate concentration of 100 μmol to below 25 μmol , or indeed the difference between the sexes, is the crucial factor. CPAF is always well established within 30 min. A small study in Oxford found that lower erythrocyte aldehyde dehydrogenase activity was associated with greater cheek temperature rise after ethanol in non-diabetic men, irrespective of the presence or absence of chlorpropamide [48].

Despite elevated acetaldehyde levels, CPAF can be blocked in some subjects by naproxen, a prostaglandin inhibitor [15]. CPAF blockade by other prostaglandin inhibitors had previously been reported with either acetyl salicylate [20] or indomethacin [19]. In this later

study, patients were selected as CPAF-positive on the basis of a substantial temperature rise ($>1.0^{\circ}\text{C}$) in a CPAF test, presumably without reference to placebo testing. It is not stated how many were on long-term chlorpropamide. Indomethacin approximately halved the cheek temperature rise in 20 diabetic patients without vascular complications at least 10 years after diagnosis, but did not affect the result in 21 diabetic patients with either proliferative retinopathy or maculopathy, or ischaemic heart disease. This was not because of differential changes in cheek temperature before drinking the sherry. The little-discussed illustration to this report strongly suggests that all 41 were a single population in regard to the relationship between the cheek temperature rise in the CPAF test and the decrease in this after indomethacin. A substantial block was seen only with the smaller temperature rises, so the result perhaps depends upon a lower initial cheek temperature, and so a greater rise after ethanol, in those with an impaired vasculature.

Nonetheless, prostaglandins were implicated in both the mechanism by which the flush develops [10] and the aetiology of both small and large blood vessel disease in diabetic patients [19], by reasoning similar to that underlying the previous announcement of 'Sensitivity to enkephalin as a cause of Type 2 diabetes' [8], still promoted 3 years later [49]. The blockade of CPAF by naloxone [8] indicated the complexity of the underlying mechanism, as well as providing a lead to disclosing the combination of chlorpropamide and alcohol as the first known stimulus increasing plasma met-enkephalin [13], in both flushers and non-flushers. Met-enkephalin is not increased by intravenous alcohol (after chlorpropamide), though that is as effective as oral alcohol in producing a flush [50]. Moreover, naloxone is neither a specific nor a comprehensive endorphin antagonist [51]. Indeed the increase in glucagon (and associated hyperglycaemia and hyperinsulinaemia) in normal subjects produced by intravenous β -endorphin has been reported to be unresponsive to attempted blockade with naloxone [52].

Changes in circulating kinin concentrations were excluded as the active agents producing CPAF in Malmö [53] but at King's College Hospital attention has now fastened on compounds with which acetaldehyde forms adducts, such as dopamine which yields the stable salsolinol, a tetrahydroisoquinoline [54]. The report of reduced urinary excretion of this should be tempered by consideration that, in the two subjects (out of five) who fainted, a reduction in glomerular filtration rate may have contributed to this observation [54].

Another possibly promising angle not yet explored is chlorpropamide's extreme position among the sulphonylureas as an effective potentiator of vasopressin [55] and so a useful treatment of the less severe cases of diabetes insipidus. Recent studies in the Brattleboro rat have shown chlorpropamide to augment the effect of vasopressin on urinary excretion of prostaglandin E_2 ,

and possibly to alter some vascular responses to vasopressin [56]. Allied with the effect of alcohol and of opiates in inhibiting release of vasopressin, itself a vasoconstrictor, hypotheses are easier to construct than to test.

Discussion of CPAF has probably under-estimated the contribution of an action of ethanol alone (doubtless via acetaldehyde) in its development, though a magnification of this by chlorpropamide is clearly important. The possibility of being positive for both stages, or just for one of them, must persist because of the limited use of placebo testing, and may underlie the distinction drawn so usefully by Jefferys and Strakosch [10] between 'definitely positive' and 'questionably positive' responses.

Conclusion

Further progress can depend only on standardised testing to determine the response precisely, after consideration of known interacting factors (e.g. initial cheek temperature, plasma chlorpropamide concentration). Until liver biopsy to identify the alcohol dehydrogenase isoenzymes becomes harmless, further studies will perhaps reveal more about the extra-pancreatic effects of one sulphonylurea than about the aetiology of Type 2 diabetes and its complications.

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