Overview:

This study [1] and the related papers, show a complexity in trying to treat nervous system issues via manipulation of glutathione. As I look at online posts people make and opinions posed it is clear that this evolving area of neurobiology needs more “fleshing out” for clinicians. This is not a bad thing – every time there is this type of confusion it indicates that new information needs to be incorporated into our existing knowledge base (and that treating human beings isn’t as easy as it looks).

Clinical Discussion:

Sometimes... being old has advantages. In the case of this study [1] it is seeing a protocol I used in the 1990’s replicated (as if some new epiphany) and assessed in a real trial setting. Nothing wrong with that at all because they now have many methods of assessment we did not have all those years ago when what we had to go on was our wits and some sparse data. The fact that our patients improved is likely a shock to modern researchers such as Monti et.al.

Modern era physicians may say “why were you using NAC in Parkinson’s (and other neurodegenerative disease) when you could use glutathione?” Excellent question, and the answer is “we did not have it (IV glutathione)”. I suppose it is like my early memories of television, all black and white with two or three channels and trying to describe that to a kid with an IPhone. So how did those of us in that generation come on to the idea of glutathione “support” for neurological disease?

The few of us doing it understood biochemistry and neurobiology enough to realize that thiols like NAC (and ALA which we were able to get for parenteral use later as well) may have a beneficial effect in the brain as well as the liver and other organs, and could support the formation of glutathione (which at the time was not really available in any form as a therapy). So protocols very much like this one (IV NAC plus oral NAC on non IV days) were developed and used. If I were asking someone from an older time who had already used this protocol my questions would be:

- Why don’t you do it any more, or do you?
- Why, if glutathione purportedly does not cross the blood brain barrier, do we not use more NAC for CNS issues?
- Do the “newer” protocols using intranasal, oral liposomal or IV glutathione really work better?
- Can we make glutathione therapy (from any substrate) more efficient and effective?
- How about all this new “SNP” knowledge. Does that have an effect?

All are excellent questions and in light of my historical background with this topic and protocol I will discuss all of them in relationship to this study. The current paper states the following conclusions: “The results of this preliminary study demonstrate for the first time a potential direct effect of NAC on the dopamine system in PD patients, and this observation may be associated with positive clinical effects. A large-scale clinical trial to test the therapeutic efficacy of NAC in this population and to better elucidate the mechanism of action is warranted.” If one reads the entire paper it is clear that this was a
reasonably designed in vitro and in vivo study. As mentioned earlier we in the past surmised these effects and used NAC (oral and IV) in this same setting. In light of that I will now answer the questions posed above.

**Why don’t you do it any more, or do you?**

As soon as IV glutathione (GSH) (and later oral liposomal or other absorbable forms) became available I and others saw better clinical results using glutathione over NAC exclusively. That said however, in those who are responsive (see SNP discussion below), I do use oral NAC and or ALA as a glutathione support in all such cases. Conversely since IV glutathione became available I have almost never ordered or used IV NAC simply because the (in my opinion anecdotally) outcomes are superior with IV glutathione.

**Why, if glutathione purportedly does not cross the blood brain barrier (BBB), do we not use more NAC (especially IV) for CNS issues?**

I would like to (hopefully) stop the misinformation on the BBB-GSH connection. I have read most of the data on this and am very convinced that (based on scientific investigation) GSH is transported as GSH across the BBB. This is not even taking into account the leaky BBB in neuro-inflammatory conditions which (even if GSH couldn’t be transported across the BBB the inflammation would allow it). But under physiologic conditions the BBB does **(yes DOES)** transport GSH into the brain circulation intact. Tsuji [2] demonstrated this in a seminal neuroscience paper and cites multiple supporting references. So yes, go ahead and use GSH.

Any GSH that makes it into the plasma can get to the brain without “being dismantled to cysteine etc. before transport” as is often unfortunately stated emphatically.

If you have lost track, the point of NAC originally as used was as a substrate for GSH (it is the rate limiting amino acid for GSH) hence the study using NAC we are reviewing. So if we can supply GSH to the brain by intranasal, IV, IM or oral methods isn’t that better?

**As a quick note:** Why use NAC in this study instead of GSH? NAC and its relative l-cysteine are approved medications by the USP and FDA. GSH is not.

**Do the “newer” protocols using intranasal, oral liposomal or IV glutathione really work better?**

I would argue, based on having done this with NAC alone or with NAC orally with IV GSH as augment, that the modern advances in GSH availability and delivery ARE an improvement on the NAC alone. No, the paper we are discussing does not discuss this. They cannot as they needed a single intervention medication. That does not make the science (or our experience with) of GSH change however.

**Can we make glutathione therapy (from any substrate) more efficient and effective?**

The tenets of improving GSH therapy are as follows: Give GSH (IV and via other noted routes) and if applicable GSH precursors (as in NAC and ALA) orally. Assure redox balance long term (as described in earlier posts) [3]. Assure GSH is supported by its many cofactors. [4] In general (unless a genomic condition precluded use) I always give NAC or ALA orally as substrate between IV or Intranasal GSH use. And in all cases I recommend cofactor use.
**How about all this new “SNP” knowledge. Does that have an effect?**

Glutathione Synthetase (GSS) and SNPs in this region are connected with poor utilization of precursors for GSH formation (such as ALA and NAC). A look to the National Library of Medicine database can provide more specifics of this SNP area as well as related pathogenic studies. [5]. The bottom line here is that the more GSS SNPs one has the more they need GSH and the less that precursors such as ALA and NAC will help.

**Clinical Summary:**

This well designed trial does show benefit directly to neurons via supplementation with NAC. Our understanding of the benefit of GSH for conditions such as Parkinson’s disease may be partly related to the GSH effect and potentially to the NAC effect. At this point we cannot know to any certainty which has what effect. What many years of clinical use of all these agents has taught me is that combination and well-rounded therapy always surpasses a single agent approach.

Supplement with parenteral, intranasal or oral GSH (my current choices are Acetyl Glutathione or Liposomal Glutathione for oral use). Supply GSH cofactors as well as ReDox triplet cofactors (see references below). And if using a non-oral form of GSH provide oral NAC or ALA between. If the patient has GSS SNP’s consider that NAC and or ALA will have much less efficacy.

References:


