

Medical Matters

The Use of Medication in the MPS Disorders

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Alexander the Great is one of my heroes. He really was a great man. He had conquered half the world by the age of 21 and was also quite sensible when it came to medical care and this is one of his famous quotes.

*“I’m dying with the aid of too many physicians”
– Alexander the Great (356BC –323BC)*

To give you some idea that whilst medication in many situations is helpful, it’s not a subject that should be taken lightly. For every medication that you prescribe for a positive effect you’ve got to remember that there is a potential negative effect. Alexander the Great had it just about right; doctors can be very dangerous people. The majority of doctors are very kind, helpful, nice and are doing the best for your child but there will be occasional times when things will go wrong.

Before treating any patient with medication a doctor must decide:

- In a person who has a rather complex disorder, should the doctor interfere with the patient at all? Is what he/she is proposing to do going to be to the patient’s benefit?
- What alteration in the patient’s state he/she hopes to achieve.
- That the drug being considered is capable of achieving that change.
- What other effects the drug may have and whether these may be harmful to the patient.
- Whether the likelihood of benefit outweighs the likelihood of damage.

There are some specific problems when dealing with MPS children.

- with other, more complex medical problems.

- In many situations it is very difficult to tell whether treatment is working, at least initially.
- The dosages often used in MPS disorders are not standard dosages. They are much higher, in some circumstances, to get the same effect.
- In children who have learning difficulties, particularly if those learning difficulties are severe, it is often very difficult to work out what is disease and what are side-effects of the medication. When adverse events occur it can be difficult to work out whether it is due to disease or the drug that has been prescribed.
- With MPS disorders there is very little literature to help one decide upon a rational approach to therapy. Often we are using medications by trial and error.

Most paediatricians are conservative in their prescribing habits. Most children’s doctors think about medication very carefully, and are less likely to prescribe medication at first contact. This is important. It means there is less risk that the child is going to be given something unpleasant but, as a group, we often deny patients access to newer therapies. For example, most paediatricians don’t use some of the newer anticonvulsants that are available, as they tend to use tried and trusted medications rather than trying something new.

There are also some problems with parents. This is two-way thing; it is not just doctors who have problems. Some parents may cause problems because:

- Often parents expect an immediate result from medication. They go to the doctor, explain the problem, the doctor says we should try this medication and when it isn’t working twelve hours later or the following day, they get upset. They often expect results of an over-ambitious nature. It is very unusual for you to go to a doctor with a problem, the doctor prescribes a drug and the problem goes away. The only exception would be an infection and antibiotics. It would be very unusual for this to happen

- The other problem is that many parents are actually non-compliant. I'm sure that you are all surprised to hear this, but there are many parents who actually don't give their children the medication. The commonest things that parents don't comply with are things like asthma treatments and epilepsy treatments. If we had an indicator test, which allowed us to take a sample of urine and detect all the different drugs in the urine, I think we'd find that many of the children for whom we think we're prescribing medication, aren't actually getting the medication.

Rather than talking about medication in general, I'd like to hone in on three particular areas, which cause problems in MPS disorders and talk about the treatment of these with medication.

1. the management of challenging behaviour
2. sleep disturbance
3. epilepsy

Challenging behaviour

What do we mean by challenging behaviour?

Challenging behaviour is:

- Hyperactive, "motor driven" behaviour, where you see children on the go with a very short attention span, flitting from object to object, subject to subject, often with no apparent purpose and non-stop.
- This is often associated in some patients with some element of physical aggressions.
- Occasionally with property destruction
- Often with the children being non-compliant with instructions and with no sense of danger.

This is a fairly typical pattern of behavior, for instance, for many of our Sanfilippo children and some of the other children with MPS. It's a very difficult problem for parents to deal with and a difficult problem for doctors to treat.

In the management of challenging behaviour, drugs are only part of the management strategy.

- Firstly, it is important to get some sort of behavioural assessment performed. Our psychology colleagues can have a look at the situation both inside and outside the home, make some form of assessment and suggest some strategies that parents can try. Although we have Challenging Behaviour Teams in the UK, their success rate with our patients is actually quite small. There are some children who do respond very well to a very carefully structured psychological approach to their behaviour management, but in my experience the number of those patients are actually very small.
- There are of course other important things you can do such as environmental modifications. This a long-winded way of saying put your television out of reach, or your video on the top shelf and don't have your breakable ornaments within reach etc.
- Equally important is to try to get a break from this type of very wearying behaviour by making sure that you do get adequate respite.
- When you have thought about all of these, you can think about whether drugs are indicated and if so which drugs should be tried?

There are many different drugs that can be tried in the treatment of challenging behaviour and they come under different categories.

1. neuroleptics
2. anxiolytics
3. anti-depressants
4. psychostimulants
5. miscellaneous

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When you see lists like this with lots of different types of drugs you know that's because not one works well. If this was a list with one drug on it you'd know that there was a wonderful treatment for challenging behaviours. Parents often find it difficult to accept that, in some circumstances, doctors (even those with

the best will in the world) are not able to successfully treat the child's challenging behaviour. It's just too difficult to treat.

1. A **Neuroleptic** medication is a medication, which produces quieting. If you are given this medication as a normal individual it makes you indifferent to your surroundings, oblivious to your surroundings, and causes slowing of your thought processes and slowing of your movements. If children have too much of this type of medication, it's when parents say, "you've turned my child into a zombie!" There are a large number of neuroleptic medications and the following are the proper names for the ones we use in the UK.

Phenothiazines:

- Chlorpromazine (*largactil*)
- Thioridazine (*melleril*)

Butyrophenones:

- Halperidon (*serenace*)

Without a doubt the most prescribed for this kind of challenging behaviour in the UK is *melleril*. The reason for this is that *melleril* has a long history of use in this situation and, compared with the others, it's pretty safe even in high dosages. It's a good medication, quite old fashioned, but a good medication nonetheless. It's certainly better than, *halperidol* although *halperidol* is the second most common drug used in this group.

It is important to remember when you use this type of medication in children that the incidence of side-effects is very common.

General side-effects:

- The most common side-effect you see is drowsiness. A common complaint by parents is that I gave him this medication and you couldn't do anything with him, he was just too quiet.
- More worrying are the movement disorders, which you sometimes see occurring as a side-effect of this type of medication. If you see children develop uncontrolled excessive motor activity then you have to stop the medication.

Less common side-effects:

- There are some other very rare complications. For instance, high dosages of *melleril* over a long period of time can damage the retina at the back of the eye, so visual loss can occur. This is not usual in the dosages that are used for MPS
- *Largactil* has a problem in that it can damage the liver and you need to keep a check with liver function tests from time to time if you use the medication.

2. The second group of drugs which are used quite commonly in patients with MPS are drugs called **anxiolytics**. These are the valium-type drugs, the benzodiazepines. Anxiolytic drugs are drugs, which suppress aggression, they sedate patients and reduce anxiety. They are also quite useful because they have anti-convulsant and muscle-relaxing properties. So, in children who have a lot of excessive motor activity, muscle spasms or twitching, this group of drugs can be very good. By far the most commonly used drug of the anxiolytic is diazepam (valium), because it is the one that doctors have the most experience with.

Side-effects:

- One of the major side-effects is the increased secretion which occurs in many patients. This can be a big problem, particularly in those children who have very poor swallowing. The secretion build-up which occurs can actually limit the use of this type of medication.
- Again, drowsiness and confusion are the commonest side-effects seen in clinical practice.

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- This is a group of drugs where you get tolerance. You tend, once you start on this preparation, to have to increase the dosage over time to get the same effect. That's not addiction; it's tolerance. The children aren't addicted to the drug, they just metabolize it faster and need a larger amount of drug to get the same effect.

- It's also important to remember if you have been on them for a long time, you must withdraw them slowly. If you stop them suddenly you put the child at risk of developing seizures. So you have to reduce this group of medications very slowly.
- Respiratory depression is another problem to watch out for.
- 3. The other drugs, which are used, are anti-depressants. **Anti-depressants** are drugs which are aimed at lightening your mood but can be useful in some children who have mood disturbance. It must be avoided in patients with difficult epilepsy. There are two common groups of anti-depressants, which are used widely for children with MPS disorders.
- Of the tricyclic anti-depressants, imipramine hydrochloride (*tofranil*) is very useful and is the treatment of choice for a particular form of epilepsy known as gelastic epilepsy. Gelastic epilepsy is epilepsy induced by laughing. So children often laugh and laugh uncontrollably and then lose their muscle tone and either drop to the ground or slump. They can injure themselves or hit their head when they do this. Gelastic epilepsy does not respond to normal anti-convulsants and is treated best by using *tofranil* or *imipramine*.
- The other group of drugs which I use quite a bit now are the serotonin re-uptake inhibitors such as fluoxetine (*prozac*). *Prozac* is very good in children with mood disturbance. Some children with MPS II and III have quite wildly fluctuating mood - they'll cry for no reason, laugh for no reason – and it will swing almost minute to minute in some children. *Prozac* can smooth that out and can generally be mood lightening in patients, with this type of disorder. It's very difficult to get over to parents that when children cry they're not crying because they are in pain. They laugh and there's no reason for them to laugh. Because laughter is a sound we associate with very positive thoughts, we ignore it but when children cry, and the stimulus to do both is the same, we get upset and very anxious and tense and want it stopped. This fluctuation can often be treated quite successfully with *prozac*.

Side-effects:

- You have to be very careful. In children who have difficult epilepsy you shouldn't use *prozac*. There is quite a body of literature which suggests that *prozac* can make the control of epilepsy worse. It is not a big problem in a child who has well-controlled epilepsy on anti-convulsants but if you have a child who has difficult to control epilepsy, on multiple anti-convulsants you ought to avoid *prozac* because it can make that treatment process even more difficult.

There are some newer serotonin re-uptake inhibitors on the market and I have no experience of those preparations at all because I am a conservative paediatrician who denies my patients new therapies!

4. The other drugs, which come in and out of fashion very frequently, in the management of hyperactivity, challenging behaviour or Attention Deficit Disorder, are the **psychostimulants**. The most commonly prescribed amphetamine-related psychostimulant in the UK is methylphenidate (*Ritalin*). This is generally used as a therapy in children who have motor-driven attention deficit disorder or hyperactivity and is probably a very over prescribed preparation in most countries. The thing to remember about *Ritalin* is that its effective dose range is extremely wide. There isn't one fixed dose, which will work in any one child.

Side-effects

- It can cause alopecia or baldness. It is a side-effect which occurs almost immediately after starting treatment so you can be reassured if your child has been on this treatment for a long time.
- 5. The other drug, which is very useful, is carbamazepine (*tegretol*). It is a very highly effective anti-convulsant as well as a very good drug for treating challenging behaviour. It is useful in treating pain, which is neurological in origin. It is the treatment of choice in several conditions where you get neuralgia or pain originating in nerves. However, you must start with a very low dosage of *tegretol* and increase it slowly or side-effects are very common.

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Side-effects:

- Causes dizziness and confusion, and ataxia with the child becoming unsteady, if children are put on too high a dosage, too quickly.
- It can also affect white blood cell count and this needs to be checked from time to time.

Sleep disturbance

Sleep disturbance is another important issue for many parents.

There are different types of sleep disturbance or insomnia and I am only going to talk about two types today. Insomnia is when:

- You have difficulty in getting off to sleep but when you sleep you actually sleep all night. You wake refreshed in the morning.
- The other type of sleep disturbance is characterized by frequent waking. This type of sleep is not refreshing.
- There are some children who exhibit a combination of both types.

Parents often exaggerate sleep disturbance. When you have been deprived of sleep it is a terrible thing. If you get parents to keep a proper diary, like an anti-convulsant diary, you can go through it with the parents and see if the medications you are using are actually working.

Sleep diaries are essential:

- Sleep diaries should be kept at least 1 week prior to starting treatment and for at least 2 weeks on the treatment. Then the treatment can be assessed.
- Often when you keep a diary, you find surprisingly that the amount of sleep the child has is usually normal in a 24-hour period but it is just very fragmented. The child sleeps when he is tired. As soon as he is refreshed he wakes up, falls asleep again, wakes up. So the amount of sleep over a 24 hour clock might be normal for the child's age, except that a lot of that sleep is not occurring at a time when the parents are asleep. This causes the problem. Children with neuro-degenerative disorders often have sleep diaries like children who are blind. The reason why we fall asleep is because of the light-dark cycle.

There is a long list of medications, which are used to treat sleep disturbance.

There is not one which will work on every child. The commonest groups are the benzodiazepine and cyclopyrrolone.

Sedatives:

Benzodiazepine:

- Nitrazepam (*mogodon*)
- Temazepam (*temazepam*)
- Lormetazepam (*lormetazepam*)

Cyclopyrrolone:

- Xopiclone (*zimovane*)

All these have side-effects including tolerance and hangover the next day. There was great hope that Xopiclone would be the wonder drug in these cases. It works well for elderly people but not as well for our children.

The next group, are the hypnotics and chloral hydrates. I haven't put any dosages here because you start with the standard dosage and work up.

Hypnotics:

Chloral and derivatives:

- Chloral hydrate (*welldorm*)
- Triclofos (*triclofos*)

Avoid barbiturate and anti-histamines because of very high incidence of side-effect.

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I never use barbiturates and antihistamines to treat sleep disturbances. In the past we have often used quite high doses of vanergan which can be very effective, but in my patients it seems to produce such a high incidence of side-effects, particularly the following day, that I don't use them at all.

Melatonin:

Most of my patients are on Melatonin to treat their sleep disturbance. Melatonin is a naturally occurring chemical synthesized from serotonin in the pineal gland in our brain and is secreted in response to the light/dark cycle important in the initiation of sleep. When it becomes dark, our pineal gland starts to secrete serotonin and this activates that part of our brain, which sends us to sleep.

It is now the drug of first choice for treating sleep disturbance in neurologically impaired children in the UK and can be highly effective in about ¾ of the children.

There are some important things about Melatonin which you need to know if you are going to use, or it won't work.

- Strict bedtime regiment, with **same sleep time every night**
- Given 30 minutes before normal sleep time to 12 hours before the child is supposed to wake
- Darkened room
- Effect within three days
- Three month trial
- Dose 2-5 mg/night – increase to 10mg if no effect in 7 days

Epilepsy

Some general points about epilepsy:

- Not all paroxysmal activity is epileptic
- There are many different seizure types and some children will have many different types of seizures
- Many different drugs used in treatment
- No consistent treatment protocols

Study results in epilepsy in MPS in the UK

I'd like to share a small study that we did in the UK. We surveyed by questionnaire 237 patients with various types of MPS:

- 148 returned (62%)
- information on 147 children

The reassuring thing is that the majority of children didn't have any seizures. Seizures occur mainly in children with MPS II or III. No children surveyed with MPS I or MPS IV had seizures. Of 36 children with Hunter syndrome, (had a history of epilepsy. Of 56 children with Sanfilippo syndrome, 21 had epilepsy. Some of the children with Sanfilippo were quite young and may develop seizures later.

Seizure type:

- primary generalized or mixed – 75% - which responds well to treatment
- partial seizures (absence or tonic) – 15%
- gelastic – 2 patients (1.5%)
- unsure – 8.5%

Drug Treatment:

- sodium valproate (*epilim*) alone – 60%
- carbamazepine (*tegritol*) alone – 20%
- together – 15%
- various including lamotrigine (*lamictal*), vigabatrin (*sabril*), imipramine (*tofranil*)

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In conclusion, medication is going to be necessary for many, many patients. Generally speaking, medicines are safe as long as they are used with caution. Both doctor and parent should be realistic in their expectations from the use of medications. There is very little literature about the use of specific drugs in MPS patients. It is important to remember that what is effective in one patient may not work in the next. Each child is an individual and should be treated as such.

