A memorial lecture

Bengt–Erik Wiholm,
MD, PhD, FRCP (London)
Beje – the person
The ‘puzzle method’
What’s a signal?
PSURs (CIOMS)
Benefit and risk
Chemical predictors
Controls?
Conclusion
The “Puzzle Method”

- Guillain-Barre syndrome following zimeldine treatment

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The ‘Puzzle method’

• “His handling of zimeldine and Guillain-Barre Syndrome (GBS) early in the 1980s was but a prelude to a career marked with innovation and insights into adverse drug reactions. With the observation of 13 cases of GBS, Wiholm's team was able to ascertain that users of zimeldine has an approximately 25-fold increased risk of the condition compared to persons not using the drug.”

• Citation on Wikipedia
The ‘Puzzle method’

SUMMARY Thirteen cases of the Guillain-Barre syndrome are reviewed, all occurring with a similar relationship to recent commencement of treatment with the antidepressive drug zimeldine.

The risk of developing Guillain-Barre syndrome was increased about 25-fold among patients receiving zimeldine, as compared with the natural incidence of the disorder. The cases described provide strong evidence that Guillain-Barre syndrome may occur as a specific, probably immunologically mediated, complication of drug therapy.
The “Puzzle method”

• **Discussion**

  “The present ten patients with an *indisputable* diagnosis of Guillain-Barre syndrome constitute a homogeneous group. They all fell ill in a similar manner, shortly after the institution of zimeldine treatment....”

  “Another three patients had similar symptoms...but did not fulfill the diagnostic criteria...”

  *Every case was investigated by neurologists with a complete history taken and they had supporting investigations*
The “Puzzle method”

• **Discussion**
  
  • *Differences in progress of symptoms was noted*
  
  “Any of the influenza-like symptoms preceding the neurological illness may have been caused by a coinciding viral infection, but the uniform temporal relationship between these symptoms and the commencement of zimeldine treatment makes such a coincidence unlikely as the major determinant of the events observed....”

  • “The cases appeared sporadically during the time period when zimeldine was on the market and there was no simultaneous epidemic of influenza....”

  • “The total dose of zimeldine was low in all patients at the time when the influenza-like reaction and the acute polyneuropathy appeared. Thus, a direct toxic effect seems unlikely...”
The “Puzzle method”

- “The annual incidence of Guillain-Barre syndrome is reported to be 1-2 per 100,000 population....”
- “Eight cases of Guillain-Barre syndrome (patients 2-9) means a 23-fold increase in the incidence. If 11 cases are accepted (thus including patients 11-13, who had a somewhat atypical clinical course), the increase will be 31-fold...”
data from a random prescription sample, are published yearly by the National Corporation of Swedish Pharmacies. Thus, data on the total sales and on the prescribed average daily dose in relation to age and sex are available for zimeldine.

**Results**

The typical course of events is illustrated by the following case history.

A 65-year-old man, a teetotaller, had suffered from psoriasis for many years, but had otherwise been healthy. He developed depressive symptoms and zimeldine, 200 mg/day, was prescribed on 18 April, 1983. On 5 May he developed fever and had pronounced muscle pains in the back and legs and a sore throat. The following day he complained of leg numbness, which deteriorated over the next few days, and weakness of the legs supervened. Neurological examination on 10 May revealed reduced sensation in all four limbs and marked weakness of the legs. The tendon reflexes in the legs were sluggish and bladder paresis was discovered, with a residual urine volume of 1000 ml. Zimeldine treatment was discontinued on 10 May. On 11 May the patient's legs were almost paralytic and no tendon reflexes could be elicited in the legs. Two days later he had regained slight ability for extension and flexion of the knees, but areflexia and inability to void persisted. Slow but steady improvement followed, and on 8 June, when he was admitted to a rehabilitation clinic, he was able to walk with the support of an accompanying person; at that time he was again able to perceive bladder distension.

The protein concentrations in the CSF were 1.40, 1.82 and 1.64 g/dl on 10 May, 18 May and 2 June, respectively (normal upper limit 0.5 g/dl). The highest CSF cell count was 6 polymorphonuclear and 2 mononuclear cells (10 May).

At electromyography on 24 May, signs of peripheral demyelination were observed in muscles of both legs. The conduction velocities of the peroneal, posterior tibial and sural nerves were normal on 11 May, but some of these nerves showed moderately slowed conduction on 24 May. (Case 5; cf Tables 1-4.)

**Summarised clinical data.** Details of the 13 reported patients are presented in tables 1, 2 and 3, including information concerning zimeldine treatment, symptoms, signs and clinical course, and results of cerebrospinal fluid (CSF) analysis and nerve conduction velocity measurements.

Within 6–17 days (mean 12.4 days) after the start of zimeldine treatment, all patients developed an acute adverse reaction to the drug, with influenza-like symptoms, mainly fever and myalgia (two patients had no myalgia). The cumulative doses of zimeldine at this time were 900–3,400 mg (mean 1,800 mg) — the recommended daily dose was 100 or 200 mg. Within a further 1–20 days (11–30 days after commencement of zimeldine treatment), all patients developed widespread, symmetrical dysfunctions of peripheral nerves with subacute onset. The cumulative doses of zimeldine were then 1,200–4,400 mg (mean 2,500 mg).

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### Table 1: **Age and sex of the patients, drug dose and course until occurrence of neurological symptoms**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Zimeldine treatment</th>
<th>Time of Initial symptoms</th>
<th>Initial symptoms</th>
<th>Time of first neurological symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Duration</td>
<td>Dose</td>
<td>Days</td>
<td>Cumulative dose</td>
</tr>
<tr>
<td>1</td>
<td>F</td>
<td>47</td>
<td>14 days</td>
<td>200 mg/d</td>
<td>11</td>
<td>14 days</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>61</td>
<td>15 days</td>
<td>200 mg/d</td>
<td>6</td>
<td>6 days</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>81</td>
<td>23 days</td>
<td>100 mg/d</td>
<td>6</td>
<td>6 days</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>49</td>
<td>22 days</td>
<td>100 mg/d</td>
<td>15</td>
<td>15 days</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>65</td>
<td>23 days</td>
<td>200 mg/d</td>
<td>17</td>
<td>17 days</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>63</td>
<td>12 days</td>
<td>100 mg/d</td>
<td>9</td>
<td>9 days</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>72</td>
<td>15 days</td>
<td>200 mg/d</td>
<td>14</td>
<td>14 days</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>79</td>
<td>25 days</td>
<td>100–200 mg/d</td>
<td>14</td>
<td>14 days</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>53</td>
<td>14 days</td>
<td>100 mg/d</td>
<td>14</td>
<td>14 days</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>68</td>
<td>14 days</td>
<td>100 mg/d</td>
<td>9</td>
<td>9 days</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>52</td>
<td>35 days</td>
<td>100 mg/d</td>
<td>14</td>
<td>14 days</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>72</td>
<td>10 days</td>
<td>100 mg/d</td>
<td>8</td>
<td>8 days</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>68</td>
<td>30 days</td>
<td>100 mg/d</td>
<td>16</td>
<td>16 days</td>
</tr>
</tbody>
</table>
Beje’s puzzle

• He called it that because he had to find information from different sources and fit so much information together, then how to:
  – Get maximum information from clinical cases
  – Make sure you have comparable cases
    • That is, do we know what we are talking about? Do we know the indication? Do we know other illnesses? Other causes?
  – Make sure drug & doses are correct, time-to-onset and total load
  – What is the background incidence? What is the variance?

• How do we put it all together?
  – and do it well enough?
The puzzle of the future of drug safety and pharmacovigilance

- I have been asked to link in a mention of the new ADIS and ISoP book
  “Pharmacovigilance: critique and ways forward”
  - Publication date first week November
Pieces of our future puzzle

- Multiple silos in health care
- Public health v individual health
- Genetics – gene expression
- Globalisation: one world harmonisation or standardisation
- What is safe? What is a signal?
- Openness – educating the public
- Negative bureaucracy
- Local networks advantageous to active PV?
- Dynamism in getting us known, and to tell stakeholders what we do
  - “Take and Tell”
- Patient viewpoint underused – Epidemico; WEB-RDR
- Traditional medicines
- Problems with observational studies
- Ecopharmacovigilance
Pharmacovigilance: Critique and Ways Forward

- Previous slide shows just some of the important issues raised in ‘Pharmacovigilance – critique and ways forward’ to come out very soon
  - Which includes issues raised mostly by ISoP members

- We have come a long way since 1985, but Beje’s puzzle method is not used fully any longer,
  - Because of time constraints and lack of clinical input??
  - And now we have much greater complexity in both data and demands from patients and health care professionals
Multimorbidity: how we can do better (NICE guidelines)
  - Medication harms and general problems with drugs mentioned 8 times
  - Medication is mentioned in 2/7 recommendations
  - Planned reviews and the issue of benefit to risk is mentioned specifically

But there is no mention of where to find relevant data and how it might help - other than to use electronic health care records
Thinking of the ‘puzzle method’

Do we do hypothesis development as well as Beje now?

We must develop our science and professional vision faster to keep up with the requirements of patients and modern medical practice.
Pharmacovigilance: Critique and Ways Forward

I think Beje would be saying let’s take a closer and critical look at how we use all the evidence we have to solve the puzzles before us in the best possible way

– He would be asking how we can get more and better data?
– How can we do benefit and risk judgements better?
– How can we use different methods to solve problems that result in suboptimal therapy?
In summary- our two future puzzles

- *IF* you agree we don’t do detailed clinical evaluations of individual cases, what do we do instead to gain a picture of adverse effects of drugs in clinical practice?
  - If we don’t do it, who will?

- How do we put together all the information we have on risk to help clinical decision making?
  - And communicate it?
He was never in time for his classes...
He wasn't in time for his dinner...
Then one day... he wasn't in his time at all.

The future is now
We should *always* remember!

*Without deviation from the norm, 'progress' is not possible.*

- Frank Zappa